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# A study of measles in adults at Charlotte Maxeke Johannesburg Academic Hospital

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# A STUDY OF MEASLES IN ADULTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg 2015

# DECLARATION

I, Nina Elisabeth Diana declare that this research project is my own work. It is being submitted for the degree of Master of Medicine in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this of any other University.

_____

9th day of February, 2015

*In loving memory*

*of my brother,*

*Matthew*

# ABSTRACT

# A STUDY OF MEASLES IN ADULTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL


## Background

Measles outbreaks continue to occur in South Africa. Whilst measles is traditionally a childhood illness, there are an increasing number of cases occurring in adults.

## Objectives

The objectives were to describe the clinical characteristics and outcomes of adult patients admitted with measles and to compare these parameters in HIV-seropositive and HIV-seronegative cases.

## Methods

A retrospective record review of adult patients confirmed to have measles admitted to the Infectious Disease Unit at Charlotte Maxeke Johannesburg Academic Hospital from 1 October 2009 to 31 March 2010 was conducted. Data collected included demographic, clinical, laboratory, radiographic parameters, and outcomes. HIV-positive and HIV-negative patients were compared with respect to the above parameters.

## Results

Overall 33 patients were included in this analysis, of whom 18 (54.5%) were female, all were of black African descent and their mean age was 27.8 ± 5.8 years. Median duration of symptoms was 4 days (range 1 – 7 days). All patients had a morbilliform rash and conjunctivitis on presentation. Twelve patients (36.4%) had a clinical course complicated by pneumonia. Six of these patients (18.2% of the total group) were admitted to ICU/High care; three of whom developed respiratory failure requiring mechanical ventilation, and acute kidney injury. Other complications included purulent conjunctivitis (3%), pancreatitis (3%) and encephalitis (3%). Median length of hospital stay was 3 days (range 1 – 31 days). Three patients (9.1%) demised. A total of 24 patients were tested for HIV infection and 18 tested seropositive. More female patients tested positive for HIV infection. HIV-infected patients had a longer length of hospital stay ($p = 0.03$).

## Conclusion

Measles continues to cause morbidity and mortality in adult patients. More severe consequences occur in HIV-positive patients.

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# ABBREVIATIONS/ NOMENCLATURE

| | |
|---|---|
| AIDS | Acquired immune deficiency syndrome |
| AKI | Acute kidney injury |
| BP | Blood pressure |
| CD4 | Cluster of differentiation antigen 4 |
| CD8 | Cluster of differentiation antigen 8 |
| CDC | Centre for Disease Control and Prevention |
| CMJAH | Charlotte Maxeke Johannesburg Academic Hospital |
| CNS | Central nervous system |
| CVS | Cardiovascular system |
| CXR | Chest x-ray |
| DOA | Date of admission |
| DOD | Date of discharge |
| EPI | Expanded Programme of Immunisation |
| HIV | Human immunodeficiency virus |
| HR | Heart rate |
| IgM | Immunoglobulin M |
| IL-12 | Interleukin-12 |
| LAD | Lymphadenopathy |
| MV | Measles virus |
| RR | Respiratory rate |
| SA | South Africa |
| SOB | Shortness of breath |
| SSA | Sub Saharan Africa |
| WHO | World Health Organization |

# 1.0 INTRODUCTION

Measles is one of the most contagious of all human viruses (1). Measles virus infects approximately 20 million people annually, with an estimated mortality of 145 700 in 2013, mainly in developing countries (2).

## 1.1 Background

The measles virus (MV) is thought to have evolved from the closely related rinderpest virus (a pathogen of cattle) in a setting where humans and cattle lived in close quarters (3). The earliest likely origin is within the 7th century (4). Historically, the first scientific description of measles is attributed to the Persian physician, Muhammad ibn Zakariya al-Razi (860-932), who considered it to be ‘more dreaded than smallpox’ because of its frequent fatal outcome. The present epidemic strain evolved at the start of the 20th century - between 1908 and 1943 (5).

The MV was initially identified in tissue culture by Peebles and Enders in 1954 (6). After isolation of the agent, efforts to develop a measles vaccine advanced rapidly, with the first successful vaccine licenced for use in human subjects in 1963 (7).

MV infects humans and has no animal reservoir; however MV infection has been documented in colonies of captive non-human primates (8).

## 1.2 Pathogenesis

Measles is caused by an enveloped RNA virus of the genus Morbillivirus and the family Paramyxoviridae (9). The virus is highly contagious, and is transmitted by droplets produced by coughing, or through contact with contaminated respiratory secretions.

Measles pathogenesis is intricate when observed in detail. Essentially, the MV invades the respiratory epithelium and replicates in both the upper and lower respiratory tracts, as well as regional lymph nodes. A primary viraemia ensues, with spread to the reticuloendothelial tissues where the MV is amplified. A second viraemia follows with spread to multiple organs including the respiratory tract, gastrointestinal tract, liver, thymus, central nervous system (CNS), and skin, causing pathologic alterations in all affected systems (10). Towards the end of the incubation period (usually 10-14 days) the viraemia peaks, coinciding with the development of a prodromal phase of high fever, coryza, conjunctivitis and cough (4). This is the time of greatest infectivity risk and 75-90% of exposed, susceptible household contacts will develop the disease. A typical maculopapular skin rash appears 3-4 days after the prodromal phase. The exanthem extends from the face and neck, to the truck and extremities, and fades slowly over subsequent days. Bluish-white Koplik spots may be seen on the buccal mucosa at the onset of the rash, these are pathognomonic. Patients usually improve by the third day after the appearance of the rash, and are completely recovered within 10 days from the onset of initial symptoms.

Measles is historically a childhood illness (1) however reports have highlighted an increasing frequency in young adults (11, 12, 13, 14).

## 1.3 Diagnosis

In endemic areas a diagnosis of measles may be confidently made if the patient clinically presents with a 2 – 4 day history of a fever with cough, coryza or conjunctivitis, followed by a typical morbilliform rash, and Koplik spots. However, in countries with low measles prevalence, the World Health Organization (WHO) recommends use of serum IgM as the standard test to confirm the diagnosis of measles (15, 16). The anti-measles IgM assay is a highly sensitive and specific test, but false positive and false negative results have been reported (4). False positive results have been attributed to acute human parvovirus B19 co-infection (17). Measles IgM antibodies are detectable shortly after the onset of the rash, and remain positive for up to 4 weeks. Antibodies may be undetectable when the exanthem first appears. The MV may be isolated in cell cultures from peripheral mononuclear cells, nasopharyngeal specimens, conjunctival swabs, and urine samples. Viral culture is infrequently performed as the virus is difficult to culture and requires specialised laboratory facilities.

## 1.4 Complications

Measles is associated with temporary, but considerable, immunosuppression resulting in an increased susceptibility to opportunistic infections. This often leads to complications such as otitis media, diarrhoea, and pneumonia which are the central determinants of morbidity and mortality (18). Approximately 1/1000 cases is complicated by post infectious measles encephalitis; subacute sclerosing panencephalitis, a gradually evolving infection of the CNS, occurs in about 1/10 000 – 1/100 000 cases (19). Paradoxically, the disease also induces a

robust MV-specific immune response, resulting in immunity that is considered to be lifelong (20).

### 1.4.1 Measles induced immunosuppression

MV infection induces an intense immune response that is associated with depressed responses to unrelated antigens (21). The most important clinical feature of MV infection appears to be the accompanying immunosuppression. It is a transient phenomenon, but may last for several weeks or even months beyond conclusion of the acute illness (22). This increased susceptibility to secondary infections accounts for the majority of the morbidity and mortality associated with MV infection (23). Numerous aberrations of the immune system have been detailed including: alterations of cytokine responses with immune modulatory effects of interleukin-10 and down regulation of interleukin-12 (IL-12); changes in lymphocyte number and function; defective antigen presentation; and modified interferon alpha/beta signalling pathways (24). IL-12 is crucial for the co-ordination of cellular immunity. Atabani et al. (25) examined cytokine production in Gambian patients with measles to determine the effect of MV on IL-12 responses in vivo. They reported IL-12 production by peripheral blood monocytes was immensely suppressed, providing a unified mechanism for many of the immunologic abnormalities associated with measles. Increased susceptibility to tuberculosis has been described after MV infection, and has been attributed to this state of immunosuppression (26). However, Lee et al. (27) examined the incidence of tuberculosis among 53 974 measles cases during the 2000-2001 Korean outbreak, and found no positive correlation between measles and tuberculosis. Non-specific, broad immune dysfunction is thought to account for the remission of autoimmune diseases that has been noted following MV infection (28, 29, 30).

## 1.5 Factors Affecting Morbidity and Mortality

The severity of MV infection is determined by a number of host and environmental factors. Historically, measles case-fatality rates have been higher in males than infected females (31). However, data regarding sex differences in measles mortality has not been consistent (32, 33). There is an increased risk of maternal complications, including death, following measles in pregnancy (34, 35). The risk of developing severe or fatal measles is greater for those younger than 5 years of age, as well as adult patients (36, 37, 38, 39). Higher case-fatality rates are seen in patients who develop measles after within-household exposure compared to patients exposed to measles outside of the household (40, 41). A larger inoculum (more intensive and prolonged exposure within the household) is likely to account for this. Other risk factors associated with measles-related morbidity and mortality include malnutrition (especially vitamin A deficiency (42)), and immunological disorders (43, 44, 45). Patients with defects in cell-mediated immunity (acquired immune deficiency syndrome (AIDS), lymphoma, or other malignancies) are at risk for progressive life-threatening MV infection (46). Case-fatality rates among young children may reach 5-15% in developing countries (47). In industrialised countries deaths resulting from MV infection are rare, although severe forms of the disease may occur (48).

## 1.6 Protective Immune Response

Protective immunity following wild-type MV infection is considered to be life-long. This was demonstrated following a MV outbreak on the isolated Faroe Islands in 1846 (49). Two measles epidemics occurred in this community 65 years apart. Adults with a history of childhood measles did not re-acquire MV infection despite re-exposure decades later. This

process is governed by the principles of the development and persistence of immunological memory, but the precise mechanisms resulting in a sustained protective immune response to MV are not completely understood. A study by Whittle et al. (50) suggested that West African children who were frequently exposed to circulating MV had subclinical boosting of their antibody titres; however there is insufficient evidence that long-term immunity requires recurrent exposure to MV. Continued circulation of MV-specific T lymphocytes and generation of MV-specific antibodies are required for immunologic memory to MV (51). Levels of anti-MV antibodies may wane with time, but the capacity to generate a rapid secondary humoral and cellular immune defence is vital to prevent re-infection. It is estimated, that due to the persistent immunity induced by MV, the virus is unable to be sustained in a population of less than 500 000 persons (52). Wild-type MV infection induces higher antibody levels than does measles vaccination (53).

## 1.7 Vaccination

In 2001, an estimated global total of more than 23 million disability-adjusted life years were lost due to measles (54).Whilst no specific treatment of measles exists, measles can be readily prevented by vaccination. The first measles vaccines were licensed in 1963 (7). Both live attenuated and inactivated (‘killed’) vaccines were approved for use in the United States. The killed measles vaccine was withdrawn in 1967 because of frequent association with atypical measles following exposure to wild-type MV. Numerous live attenuated measles vaccines have been developed and are currently in use worldwide. The measles vaccine is equally effective against all wild-type MV genotypes. The vaccine results in both humoral and cellular immune responses comparable with those following natural infection, even though the resultant antibodies titres are usually lower. Data indicates that in persons who received

two doses of the measles vaccine, 95 - 99% developed anti-MV antibodies. The presence of neutralising antibodies is believed to be an accurate predictor of protection against infection. Vaccine-induced immunity appears to be persistent and seemingly lifelong in most persons. The measles-vaccine virus, like the wild-strain MV induces both stimulating and suppressive effects on the cell-mediated immune system. However, immune suppression following measles vaccination only persists for a few weeks and is considered innocuous, even for patients co-infected with undiagnosed tuberculosis or asymptomatic human immunodeficiency virus (HIV) (55). Adverse events subsequent to measles vaccination are usually minor and transitory, occurring in <5% of patients (56). Fever, generalised rash, and inoculation site discomfort are most frequently noted. There are no documented reports of person-to-person transmission of measles-vaccine virus.

Measles vaccination is considered to be one of the 'most cost-effective health interventions' ever developed (57, 58). Worldwide coverage of the first dose of the measles vaccine reached 82% in 2007. A subsequent drop in the worldwide estimated number of deaths from measles (750 000 to 197 000 cases) occurred between 2000 and 2007 (59). High levels of vaccine coverage provide herd immunity, thus reducing the risk of measles exposure, and conferring protection to those who are unable to be vaccinated. Herd immunity is estimated to occur at a population immunity range of 92-95% (60). Therefore, in societies with numerous unvaccinated persons, herd immunity will not provide adequate protection (61). However, there have been reports of measles outbreaks in secondary schools even though more than 95% of the students had documented measles immunity (62). Failure to sustain high levels of childhood vaccination has resulted in resurgence of the disease in nations where MV inoculation had previously drastically diminished the incidence of MV infection (63, 64, 65).

Measles remains a relevant cause of morbidity and mortality in developing countries with constrained health resources.

The measles vaccine is a live attenuated vaccine and thus may pose a risk in immunocompromised patients. The safety and efficacy of measles vaccine in HIV-seropositive adults is not well documented. A report described a case of fatal pneumonitis in a severely immunocompromised adult following measles vaccination (66). Vaccine-induced protective antibody production may also be inadequate (67). However, serious adverse effects have not been reported in HIV-seropositive patients without advanced immunosuppression who received the measles vaccine (68, 69, 70). The CDC recommends measles vaccination for all HIV-infected adults with CD4 counts of >200 cells/μL who lack evidence of measles immunity (71). Susceptible close contacts should be inoculated in order to minimise the risk of exposure of HIV-infected persons to measles (72).

# 1.8 Factors Affecting Measles Virus Transmission

## 1.8.1 Migration

Otten et al. (73) highlighted the impact of migration on measles transmission in sub-Saharan Africa (SSA). Unvaccinated children moving between bordering countries, that had failed to execute mass measles vaccination drives, were linked by epidemiological analysis to measles outbreaks in Cameroon and Burkina Faso. This finding demonstrates that sustained progress towards measles elimination in SSA will only be achievable if mass measles vaccination campaigns are co-ordinated in adjoining countries.

## 1.8.2 HIV co-infection

Measles and HIV are both endemic in SSA. Reports of measles in persons co-infected with HIV document uncharacteristic clinical findings and serious complications. In particular, several case reports have detailed an absent, delayed, or unusual rash, and the frequent development of measles pneumonitis in HIV co-infected children and adults (48, 74, 75, 76). MV encephalitis has also been reported in HIV-infected individuals (77, 78). The MV was observed in the central nervous system (CNS) of three of thirteen HIV-infected patients, and none of the five HIV-uninfected patients in an autopsy study of adult measles patients in the Ivory Coast (79). Atypical findings of measles in HIV-positive persons may lead to the diagnosis of measles being overlooked, thus increasing the risk of MV transmission. Nosocomial acquisition of measles by HIV-infected patients has been described (80). Comparative data for HIV-infected and uninfected children, in developing countries are not consistent. Measles case-fatality rates were notably high for HIV-positive children in Zambia (81), but in the former Zaire case-fatality rates were not substantially different between HIV-infected and uninfected children (82). The correlation between the severity of measles and the extent of HIV-induced immunosuppression has not been well characterised. A literature review found no clear relationship between measles severity or complication rates and CD4 cell counts or CD4:CD8 ratios (83). Given the grievous outcome of measles in HIV-infected persons with advanced disease, the World Health Organization (WHO) recommends that the measles vaccination routinely be administered to susceptible, asymptomatic HIV-infected children and adults (84). The WHO also advises that vaccination be considered for persons with symptomatic HIV infection if they are not severely immunocompromised, defined by conventional means. However, data suggests that vaccination of HIV-infected persons may not induce satisfactory protective immunity against MV (85, 86) and that measles antibody titres appear to decline more rapidly, than in the immunocompetent population (87, 88). No

relationship has been established between slope of antibody decline and CD4 lymphocyte count. Measles seroprevalence studies in HIV-infected adults propose that if MV vaccination or natural infection occurred before the subjects became HIV-seropositive; the measles specific antibody is not usually lost despite progressive HIV-induced immunosuppression (89). Even though studies suggest that MV vaccination is less effective at preventing disease in HIV-positive persons it still provides protection from serious disease and reduces the mortality rates of measles in this cohort. Intense cellular immune suppression is thought to be a risk factor for developing disease after administration of the live attenuated measles vaccine. Thus the vaccine is not recommended for HIV-infected children and adults with advanced immunosuppression, as defined by CD4 lymphocyte counts.

The impact of MV infection on the course of HIV infection has only been investigated in a few studies. Concurrent infection with measles and HIV, two immunosuppressive viruses, was predicted to exacerbate both infections (83). However, evidence suggests that co-infection results in transient suppression of HIV replication. Moss et al. (90) reported blood HIV RNA levels, in HIV-infected children living in Zambia, were significantly lower during acute measles infection when compared to HIV-infected children who did not have measles. This was confirmed by a 2008 study in HIV-infected Ugandan children (91). Whilst the precise mechanism resulting in this finding remains unclear (92); a similar suppression of HIV RNA levels is seen with corticosteroid use and is postulated to be due to a reduction in lymphocyte number (93, 94). Co-infection has been associated with prolonged shedding and delayed clearance of the MV (95), thus persons co-infected with HIV may be unrecognised MV transmitters, further thwarting eradication efforts. Other factors affirming the theory that the HIV epidemic may enhance dissemination of measles include the high rates of primary

and secondary measles vaccine failure, as well as atypical presentations resulting in delayed diagnosis in HIV-infected individuals.

## 1.9 Measles in Southern Africa

Measles is a notifiable disease in South Africa (SA). As measles is a highly contagious but vaccine-preventable disease, childhood vaccination is a critical preventative strategy. In SA, children receive the measles vaccine as part of the SA-Expanded Program of Immunisation (EPI) schedule at 9 months of age, and then a second measles vaccination at 18 months of age. Following this two-dose vaccination schedule, 95% of children will develop protective antibodies (96, 97). Achieving and sustaining high measles vaccination coverage can lead to virtual elimination of measles within a region. This was seen following the implementation of a measles elimination/eradication initiative since 1996 by seven Southern African countries, including SA (98). SA used the Pan American Health Organization strategy (99), and conducted a countrywide vaccination drive in 1996 and 1997, with the aim of eliminating measles by 2002. All children aged 9 months to 14 years were targeted, and 85% administrative coverage was achieved. A further vaccination campaign in 2000, reported 92% administrative coverage. Measles cases declined from 60 000 in 1996, to 117 laboratory-confirmed cases in 2000. There was also a drop in reported deaths from measles: 166 in 1996 to zero in 2000. This data reveals the success of the vaccination campaign (98). However, in SA between July 2003 and November 2005, 1 676 confirmed cases of measles were reported. McMorrow et al. (100) detailed the specifics of this outbreak, noting that the MV was re-introduced into Mpumalanga and Gauteng, from Mozambique. They concluded that the primary cause of the outbreak was the failure to maintain adequate vaccination rates to prevent endemic measles transmission, and thus allowing for sizeable outbreaks in

susceptible individuals when the virus was re-introduced. They also investigated the role HIV played in the outbreak and deduced that despite the possibility that vaccine effectiveness may have been reduced in HIV-infected children; the population vaccine effectiveness remained high.

The 2009/2010 South African measles outbreak resulted in 18 359 laboratory-confirmed cases reported to the National Institute of Communicable Diseases by the end of December 2010. Possible reasons identified for this outbreak include 'gaps' in the implementation of control strategies, such as: a decline in routine immunisation coverage; inability to reach all children/susceptible adults through the immunisation program; certain groups of the population refusing to immunise their children; as well as the effects of migration on measles transmission and control. The majority of cases occurred from week 37 (2009) to week 24 (2010). To restrict the impact of measles outbreaks, the WHO advocates surveillance for early detection, and rapid responses such as the expanded use of the measles vaccine (101). In SA, between 12 and 23 April 2010 a mass vaccination campaign was undertaken targeting at risk children between the ages of 6 months and 15 years. Following this campaign, a distinct reduction in the number of reported measles cases was noted. There were only 91 confirmed cases of measles countrywide during 2011 (102).

Much of the published measles-related literature focusses on the paediatric population in whom infection is more common. There are three articles relating to the South African 2009/2010 outbreak, all from the Western Cape. One describes the dermatological manifestations in children (103). The second examines the outbreak experienced by a paediatric hospital (104) and the final report describes eight cases of subacute measles encephalitis in immune-compromised adults (105).

## 1.10 Measles Outbreaks in 2013/2014

International outbreaks have been reported during 2013/2014 in the following countries:

- USA - 610 cases in 2014
- United Kingdom - 3 308 cases in 2013; 842 cases in 2014
- France - 497 cases
- Spain - 255 cases
- Netherlands - 1 162 cases
- Romania - 3 658 cases
- Pakistan - over 25 000 cases
- Philippines – 6016 cases
- Australia – 151 cases in 2013; 194 cases in 2014
- New Zealand – 113 cases in 2014
- Japan – 232 cases in 2013; 324 cases in 2014

In developed countries, the index case is usually an infected individual importing the virus from beyond the borders. The majority of the subsequent cases then occur in persons who are unvaccinated or have unknown vaccination status.

## 1.11 Conclusion

Measles causes significant morbidity and mortality worldwide yet it is highly preventable. Whilst significant progress has been made, global eradication remains the only way to assure outbreaks will no longer threaten worldwide populations.

# 2.0 MATERIALS AND METHODS

## 2.1 Study Aim

The main aim of this study was to describe the clinical characteristics, laboratory and radiological findings, and outcome of measles in adult patients admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) during the peak of the 2009/2010 epidemic to better understand the disease profile of adult patients presenting with measles.

## 2.2 The Study Objectives:

- Describe the demographic, clinical, laboratory, and radiographic features of measles occurring in adult patients admitted to a teaching hospital in Johannesburg.
- Describe the outcome of patients with regards to length of hospital stay, complications, and mortality.
- Compare demographic, clinical, laboratory, and radiographic features, as well as, outcome (length of hospital stay, complications and mortality) between HIV- infected and HIV-uninfected patients.

# 2.3 Methods

This section describes the methodology of the study.

## 2.3.1. Research design

This study was a retrospective record review.

## 2.3.2. Location of study

The study was conducted in the Infectious Disease Unit (ward 497) at the Charlotte Maxeke Johannesburg Academic Hospital.

## 2.3.3. Study participants

The study participants were consecutive adult patients hospitalised and confirmed to have measles during the period 1 October 2009 to 31 March 2010.

## 2.3.4. Data collected

Data recorded included demographic, clinical, laboratory, radiographic and outcome parameters (Appendix A: Data Collection Sheet).

## 2.3.5. Ethical considerations

Permission to conduct the study has been obtained from the Human Research Ethics Committee of the University of Witwatersrand, Clearance Certificate M10104 (Appendix B).

## 2.4 Data Analysis

Mean, median, and range was used to describe continuous data. Normally distributed data were reported as mean ± standard deviation, while data not normally distributed were reported as median and range. Categorical data were expressed as numbers (percentage and frequency). The HI- infected and HIV-uninfected group were compared using the Mann Whitney U test for continuous variables, and the Fisher's Exact (2-tail) test for categorical variables.

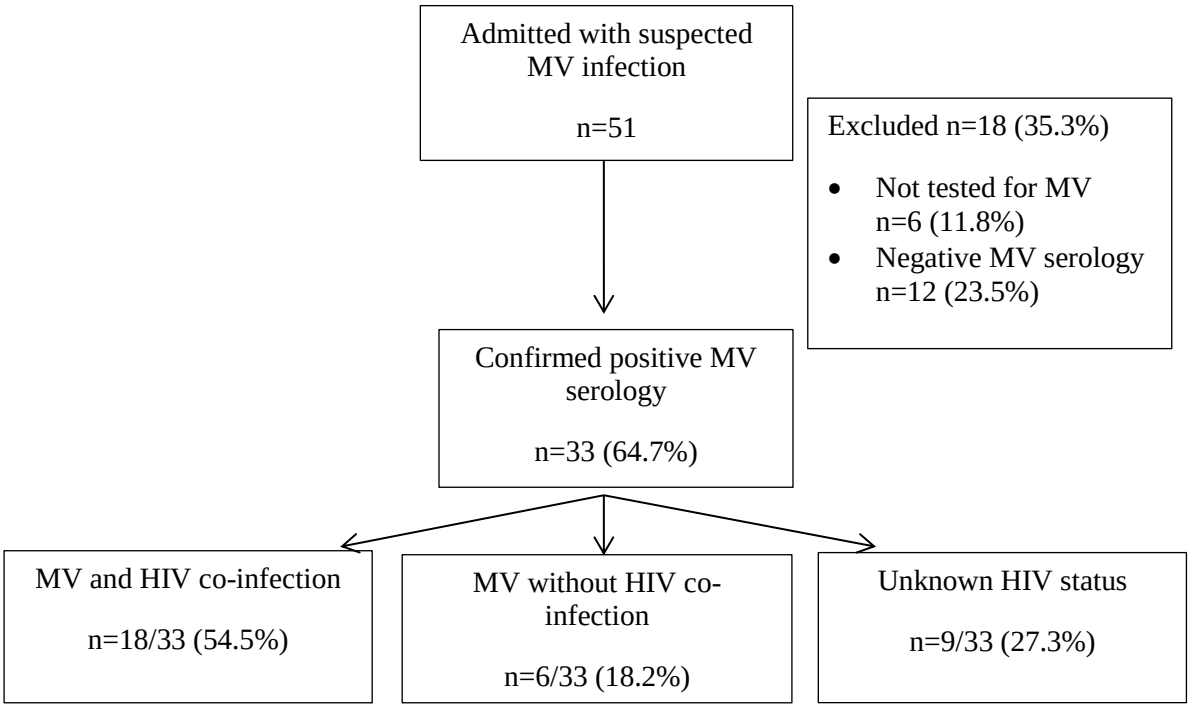
Analyses were done using GraphPad InStat version 3. All statistical tests were 2-sided and $p<0.05$ was considered statistically significant.

# 3.0 RESULTS

## 3.1 Study Population

A total of fifty one adult patients with suspected measles were admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Infectious Disease Unit between 29 September 2009 and 04 March 2010. Thirty three (64.7%) of these patients were confirmed to have measles by serology. In twelve patients (23.5%) measles serology was negative and six patients (11.8%) were not tested. The thirty three patients confirmed to have measles by serology were included in this study. Figure 1 shows the study population included in this analysis.

Figure 3.1 Flow diagram of study participants



## 3.2 Demographic Data

The mean age of the patients included in the study was 27.8 ± 5.8 years (32 patients had this data available). Fifteen patients (45.5%) were male and 18 (54.5%) female. All patients were of African origin. There were 18 (54.5%) South Africans, 13 (39.4%) Zimbabweans, and 2 patients (6.1%) from Malawi (Table 3.1).

Table 3.1 Demographic data of patients confirmed to have measles

| | | | Number of patients with data |
|---|---|---|---|
| Age (years) | | 27.8 ± 5.8 | 32 |
| Gender | Male | 15 (45.5%) | 33 |
| | Female | 18 (54.5%) | |
| Race | Black African | 32 (100%) | 32 |
| Nationality | South African | 18 (54.5%) | 33 |
| | Zimbabwean | 13 (39.4%) | |
| | Malawian | 2 (6.1%) | |

## 3.3 History

### 3.3.1 Past history

None of the patients reported previous measles infection. Only 1 (10%) of the 10 patients questioned reported having had a measles contact. Two (16.7%) of the 12 patients questioned remember being vaccinated against measles. Eight (40%) of the 20 patients questioned had children within their household. Three (18.8%) of 16 patients had visited a healthcare facility within the past month (Table 3.2).

Table 3.2 Past history of confirmed measles cases

| Past history | n/N* | % |
|---|---|---|
| Measles contact | 1/10 | 10 |
| Previous measles | 0/33 | 0 |
| Vaccination | 2/12 | 16.7 |
| Children in household | 8/20 | 40 |
| Visited hospital in past month | 3/16 | 18.8 |

*n denotes the number of patients with a positive response, N is the number of patients in whom the past history was recorded

## 3.3.2 Presenting symptoms

Median duration of symptoms was 4 days (range 1 – 7 days). All patients reported a rash and red eyes. Thirty one patients (93.9%) reported a fever, 24 (72.7%) a cough and 18 (54.5%) experienced coryza. No patients presented with complaints of yellow eyes, bleeding or seizures (Table 3.3).

Table 3.3 Presenting symptoms of confirmed measles cases

| Presenting symptoms | n/N* | % |
|---|---|---|
| Rash | 33/33 | 100 |
| Red eyes | 33/33 | 100 |
| Fever | 31/33 | 93.9 |
| Cough | 24/33 | 72.7 |
| Coryza | 18/33 | 54.5 |
| Vomiting | 8/23 | 34.8 |
| Headache | 5/30 | 16.7 |
| Confusion | 3/30 | 10 |
| Diarrhoea | 2/26 | 7.7 |
| Shortness of breath | 2/33 | 6.1 |
| Abdominal pain | 1/26 | 3.8 |
| Oral sores | 1/30 | 3.3 |

*n denotes the number of patients in whom the symptom was present, N is the number of patients in whom presence or absence of the symptom was recorded

# 3.4 Examination Findings

## 3.4.1 Vital signs

Median temperature was 39°C (range 37 - 40°C). Mean systolic blood pressure was 113.4 ± 16.8 mmHg, diastolic blood pressure was 70.5 ± 3.4 mmHg, and heart rate was 117.4 ± 23.4 beats per minute. Mean respiratory rate was 31.9 ± 6.6 breaths per minute (12 patients had data) (Table 3.4).

Table 3.4 Examination findings of confirmed measles cases: vital signs

| Vitals | | |
|---|---|---|
| Temperature (°C) | | 39 (range 37-40) |
| Blood pressure (mmHg) | Systolic | 113.4 ± 16.8 |
| | Diastolic | 70.5 ± 13.4 |
| Heart rate (beats/min) | | 117.4 ± 23.4 |
| Respiratory rate (breaths/min)[1] | | 31.9 ± 6.6 |

*Normally distributed data is reported as mean ± SD, non-normally distributed data as median (range)
[1] Data available for 12 patients

## 3.4.2 Presenting features on examination

All patients had a rash and conjunctivitis on presentation. Ten patients (30.3%) had lymphadenopathy, 8 (24.2%) displayed oral thrush and 7 (21.2%) had Koplik spots. Three patients (9.1%) were confused. Abnormal chest examination was found in 12 patients (36.4%); eleven had crackles and 1 had bronchial breathing. No patients presented with jaundice or otitis media (Table 3.5).

Table 3.5 Examination findings of confirmed measles cases: physical examination

| Examination finding | | N | % |
|---|---|---|---|
| Rash | | 33 | 100 |
| Conjunctivitis | | 33 | 100 |
| Lymphadenopathy | | 10 | 30.3 |
| Oral thrush | | 8 | 24.2 |
| Koplik spots | | 7 | 21.2 |
| Confusion | | 3 | 9.1 |
| Chest examination | Crackles | 11 | 33.3 |
| | Bronchial breathing | 1 | 3 |

# 3.5 Laboratory Investigations

Available laboratory data for the patients confirmed to have measles is documented in Table 3.6.

Of the 33 patients, 24 underwent HIV testing. This documented 18 patients to be HIV-positive and 6 patients to be HIV-negative. The HIV status of the remaining 9 patients was unknown. Comparative data of the HIV-positive and HIV-negative patients is described later.

Table 3.6 Laboratory results of confirmed measles cases

| | | | Number of patients with data |
|---|---|---|---|
| White cell count (cells $x10^9$/l) | | 6.6 ± 2.6 | 33 |
| Haemoglobin (g/dl) | | 13.7 ± 2.3 | 33 |
| Platelet count (cells $x10^9$/l) | | 180 ± 48 | 33 |
| | | | |
| Sodium (mmol/l) | | 135 (range 122-141) | 33 |
| Potassium (mmol/l) | | 3.9 ± 0.6 | 33 |
| Bicarbonate (mmol/l) | | 22.5 ± 3.5 | 33 |
| Urea (mmol/l) | | 6.4 (range 2.0 – 26.2) | 33 |
| Creatinine (µmol/l) | | 105.9 ± 47.7 | 33 |
| | | | |
| Albumin (g/l) | | 35.7 ± 6.3 | 26 |
| | | | |
| CRP | | 117 ± 72.7 | 30 |
| | | | |
| HIV | Positive | n=18 | 33 |
| | Negative | n=6 | |
| | Unknown | n=9 | |
| $CD_4$ (cells/$mm^3$) | | 109 (range 18 – 599) | 16 |
| HIV viral load (copies per ml) | | 15000 (range 0 – 500000) | 7 |

| Other investigations | | Number of patients with data |
|---|---|---|
| Lumbar puncture | All within normal limits | 5 |
| Blood cultures | All showed no growth | 17 |
| Sputum culture | *Klebsiella pneumoniae* | 2 |
| Rubella serology (IgM) | All negative | 33 |

*Normally distributed data is reported as mean ± SD, non-normally distributed data as median (range)

# 3.6 Radiological Findings

Chest x-ray (CXR) findings were documented in the bed letters of ten patients (30.3%). Five x-rays showed bilateral pulmonary infiltrates, three showed consolidation, one a pulmonary nodule and one x-ray appeared within normal limits (Table 3.7).

Table 3.7 Radiological findings in confirmed measles cases

| CXR finding | n/N* | % |
|---|---|---|
| Bilateral pulmonary infiltrates | 5/10 | 50 |
| Consolidation | 3/10 | 30 |
| Pulmonary nodule | 1/10 | 10 |
| Normal | 1/10 | 10 |

*n denotes the number of patients in whom the radiological feature was present, N is the number of patients in whom presence or absence of the radiological feature was recorded

# 3.7 Complications

Twelve patients (36.4%) had a clinical course complicated by pneumonia. Six of these patients (18.2% of the total group) were admitted to ICU/High care, three of which developed respiratory failure requiring mechanical ventilation and acute kidney injury (9.1%). Other complications included purulent conjunctivitis (3%), pancreatitis (3%) and encephalitis (3%) (Table 3.8).

Table 3.8 Complications of confirmed measles cases

| Complication | N | % |
|---|---|---|
| Pneumonia | 12 | 36.4 |
| ICU/ high care admission | 6 | 18.2 |
| Respiratory failure | 3 | 9.1 |
| Mechanical ventilation | 3 | 9.1 |
| Acute kidney injury | 3 | 9.1 |
| Purulent conjunctivitis | 1 | 3 |
| Pancreatitis | 1 | 3 |
| Encephalitis | 1 | 3 |

## 3.8 Treatment Received

Thirty one patients (93.9%) received amoxicillin – clavulanic acid, 4 patients (12.1%) received azithromycin. Other antibiotics administered included erythromycin, ceftriaxone and piperacillin – tazobactam. Thirty patients (90.9%) received vitamin A. Eight patients (24.2%) received corticosteroids, six of these patients were treated in ICU/ high care (Table 3.9).

Table 3.9 Treatment received by confirmed measles cases

| Treatment received | N | % |
|---|---|---|
| Amoxicillin – clavulanic acid | 31 | 93.9 |
| Azithromycin | 4 | 12.1 |
| Vitamin A | 30 | 90.9 |
| Corticosteroids | 8 | 24.2 |

Other medication administered included ceftriaxone, erythromycin and piperacillin-tazobactam

## 3.9 Outcome

Median length of hospital stay was 3 days (range 1 – 31 days). Thirty patients (90.9%) were discharged and three patients (9.1%) died (Table 3.10).

Table 3.10 Outcome of confirmed measles cases

| | |
|---|---|
| Length of hospital stay (days) | 3 (range 1 – 31) |
| Discharged, N (%) | 30 (90.9%) |
| Death, N (%) | 3 (9.1%) |

## 3.10 Comparison of HIV-Positive vs. HIV-Negative Patients

There were 18 HIV-positive patients and 6 HIV-negative patients. The HIV status of the remaining 9 patients was unknown.

### 3.10.1 Demographic data

Mean age of the HIV-positive patients was 28.1 ± 5.6 years and mean age of the HIV-negative group was 29.6 ± 9.0 years (p=0.74). In the HIV-positive group there were 6 males and 12 females compared to 5 males and 1 female in the HIV-negative group. There were 11 South Africans and 7 Zimbabweans in the HIV-positive group and 3 South Africans and 3 Zimbabweans in the HIV-negative group (Table 3.11).

Table 3.11 Demographic data: HIV-positive vs. HIV-negative groups

| | | HIV-positive patients | HIV-negative patients | P |
|---|---|---|---|---|
| N | | 18 | 6 | |
| Age (years) | Mean ± SD | 28.1 ± 5.6 | 29.6 ± 9.0 | 0.74 |
| Gender | Male | 6 | 5 | 0.06 |
| | Female | 12 | 1 | |
| Nationality | South African | 11 | 3 | |
| | Zimbabwean | 7 | 3 | |
| | Malawian | 0 | 0 | |

## 3.10.2 History

### 3.10.2.1 Past history

Eight patients in the HIV-positive group and 2 in the HIV-negative group were questioned regarding having a measles contact, only 1 HIV-positive patient gave a positive response. No patients reported having had previous measles. Two HIV-positive patients report being vaccinated against measles (Table 3.12).

Table 3.12 Past history: HIV-positive vs. HIV-negative groups

| Past history | HIV-positive patients | HIV-negative patients | p |
|---|---|---|---|
| | n/N* | n/N* | |
| Measles contact | 1/8 | 0/2 | 1.0 |
| Previous measles | 0/18 | 0/6 | |
| Vaccination | 2/9 | 0/2 | 1.0 |

*n denotes the number of patients with a positive response, N is the number of patients in whom the past history was recorded

### 3.10.2.2 Presenting symptoms

Median duration of symptoms was 4 days (range 1 – 7 days) for the HIV-positive group (16 patients had data) and 3 days (range 3 – 6 days) for the HIV-negative group (5 patients had data); not significantly different ($p = 0.73$).

There were no differences in the presenting symptoms when comparing the two patient groups although more of the HIV-uninfected patients presented with vomiting (not significantly different) (Table 3.13).

Table 3.13 Presenting symptoms: HIV-positive vs. HIV-negative groups

| | | HIV-positive patients | HIV-negative patients | p |
|---|---|---|---|---|
| Duration of symptoms | N[1] | 16 | 5 | |
| | Median (days) | 4 (range 1 - 7) | 3 (range 3 – 6) | 0.73 |

| Presenting symptom | n/N* | % | n/N* | % | p |
|---|---|---|---|---|---|
| Fever | 17/18 | 94.4 | 6/6 | 100 | 1.0 |
| Rash | 18/18 | 100 | 6/6 | 100 | 1.0 |
| Red eyes | 18/18 | 100 | 6/6 | 100 | 1.0 |
| Coryza | 9/18 | 50 | 3/6 | 50 | 1.0 |
| Cough | 11/18 | 61.1 | 6/6 | 100 | 0.13 |
| Shortness of breath | 2/18 | 11.1 | 0/6 | 0 | 1.0 |
| Oral sores | 1/18 | 5.6 | 0/5 | 0 | 1.0 |
| Vomiting | 3/16 | 18.8 | 3/4 | 75 | 0.06 |
| Diarrhoea | 2/17 | 11.8 | 0/4 | 0 | 1.0 |
| Abdominal pain | 1/17 | 5.9 | 0/4 | 0 | 1.0 |
| Headache | 1/18 | 5.6 | 2/6 | 33.3 | 0.22 |
| Confusion | 3/18 | 16.7 | 0/6 | 0 | 0.55 |

[1]N = number of cases with available data
*n denotes the number of patients in whom the symptom was present, N is the number of patients in whom presence or absence of the symptom was recorded

## 3.10.3 Examination findings

### 3.10.3.1 Vital signs

Vital signs for the HIV-positive and HIV-negative groups are depicted in the table below (Table 3.14). No differences were noted when comparing the parameters in the two groups of patients.

Table 3.14 Vital signs: HIV-positive vs. HIV-negative groups

| Vitals | | HIV-positive patients | HIV-negative patients | P |
|---|---|---|---|---|
| N[1] | | 18 | 6 | |
| Temperature (°C) | | 39 (range 37.5 – 40) | 39 (range 37 – 39) | 0.1 |
| Blood pressure (mmHg) | Systolic | 103.5 (range 90 – 149) | 123.5 (range 103–129) | 0.13 |
| | Diastolic | 69.5 (range 40 – 99) | 75 (range 67 – 79) | 0.42 |
| Heart rate (beats/min) | | 124 ± 23 | 105 ± 23 | 0.10 |
| Respiratory rate (breaths/min) | N[1] | 9 | 1 | |
| | | 32 ± 7.513 | 28 | Too few values |

[1]N = number of cases with available data
*Normally distributed data is reported as mean ± SD, non-normally distributed data as median (range)

### 3.10.3.2 Presenting features on examination

There were no significant differences documented between the two groups of patients with regard to clinical findings (Table 3.15).

Table 3.15 Presenting features on examination: HIV-positive vs. HIV-negative groups

| Examination finding | | HIV-positive patients | | HIV-negative patients | | p |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| Rash | | 18 | 100 | 6 | 100 | 1.0 |
| Conjunctivitis | | 18 | 100 | 6 | 100 | 1.0 |
| Koplik spots | | 5 | 27.8 | 1 | 16.7 | 1.0 |
| Oral thrush | | 6 | 33.3 | 0 | 0 | 0.28 |
| Lymphadenopathy | | 6 | 33.3 | 2 | 33.3 | 1.0 |
| Confusion | | 3 | 16.7 | 0 | 0 | 0.55 |
| Chest examination | Crackles | 5 | 27.8 | 1 | 16.7 | 1.0 |
| | Bronchial breathing | 1 | 5.6 | 0 | 0 | 1.0 |

## 3.10.4 Laboratory investigations

Routine laboratory data are shown in the table below (Table 3.16). There were no significant differences in the measured laboratory parameters between the two patient groups.

Table 3.16 Laboratory results: HIV-positive vs. HIV-negative groups

| | HIV-positive patients | HIV-negative patients | p |
|---|---|---|---|
| N[1] | 18 | 6 | |
| White cell count (cells x$10^9$/l) | 6.6 (range 4 – 14.8) | 6.9 (range 5.8 – 16) | 0.40 |
| Haemoglobin (g/dl) | 13.1 (range 9.3 - 16.3) | 16.5 (range 9.6 – 17.4) | 0.11 |
| Platelets (cells x$10^9$/l) | 187.7 ± 53.9 | 183.0 ± 49.9 | 0.87 |
| Sodium (mmol/l) | 135.5 (range 122 – 140) | 132.5 (range 126 – 141) | 0.24 |
| Potassium (mmol/l) | 4.0 ± 0.6 | 4.0 ± 0.6 | 0.97 |
| Bicarbonate (mmol/l) | 21.7 ± 3.4 | 23.8 ± 3.5 | 0.23 |
| Urea (mmol/l) | 9.6 ± 6.1 | 7.2 ± 2.3 | 0.18 |
| Creatinine (µmol/l) | 117.9 ± 55.2 | 100.5 ± 45.7 | 0.46 |

| | | | | |
|---|---|---|---|---|
| Albumin (g/l) | N[1] | 17 | 4 | |
| | | 36.1 ± 6.2 | 34.3 ± 6.7 | 0.65 |
| CRP | N[1] | 17 | 5 | |
| | | 120.8 ± 74.9 | 110.6 ± 58.5 | 0.76 |

[1] N = number of cases with available data
*Normally distributed data is reported as mean ± SD, non-normally distributed data as median (range)

## 3.10.5 Radiological findings

None of the HIV-negative patients had radiological findings documented in their records. Of the six HIV-positive patients who had findings of a CXR noted within their bed letter, three showed bilateral pulmonary infiltrates, one showed consolidation, one a pulmonary nodule and one x-ray was within normal limits (Table 3.17).

Table 3.17 Radiological findings: HIV-positive vs. HIV-negative groups

| CXR findings | HIV-positive patients | HIV-negative Patients |
|---|---|---|
| | n/N* (%) | n/N* (%) |
| Bilateral pulmonary infiltrates | 3/6 (50%) | 0/0 |
| Consolidation | 1/6 (16.7%) | 0/0 |
| Pulmonary nodule | 1/6 (16.7%) | 0/0 |
| Normal | 1/6 (16.7%) | 0/0 |

*n denotes the number of patients in whom the chest x-ray finding was present, N is the number of patients in whom chest x-ray findings were recorded

## 3.10.6 Complications

Only one HIV-negative patient had a complication (pneumonia) during their disease course. Nine HIV- positive patients developed complications. Six had a course complicated by pneumonia; five of these patients were admitted to ICU/high care, three of whom developed respiratory failure, requiring mechanical ventilation, as well as acute kidney injury. Other complications in the HIV-positive group included purulent conjunctivitis, pancreatitis and encephalitis (Table 3.18). There was no statistical difference between the two groups with respect to number of complications.

Table 3.18 Complications: HIV-positive vs. HIV-negative groups

| Complication | HIV-positive patients | HIV-negative patients |
|---|---|---|
| | N (%) | N (%) |
| Pneumonia | 6 (33.3) | 1 (16.7) |
| ICU/ high care admission | 5 (27.8) | 0 |
| Respiratory failure | 3 (16.7) | 0 |
| Mechanical ventilation | 3 (16.7) | 0 |
| Acute kidney injury | 3 (16.7) | 0 |
| Purulent conjunctivitis | 1 (5.6) | 0 |
| Pancreatitis | 1 (5.6) | 0 |
| Encephalitis | 1 (5.6) | 0 |

## 3.10.7 Treatment received

Amoxicillin – clavulanic acid was the most frequently administered initial antibiotic, being given to 17 (94.4%) of the HIV-positive patients and 5 (83.3%) of the HIV-negative patients. Two HIV-positive patients and one HIV-negative patient received azithromycin. Seventeen and five patients received vitamin A in HIV-positive and HIV-negative groups respectively. Six HIV-positive patients and one HIV-negative patient received corticosteroids (Table 3.19).

Table 3.19 Treatment received: HIV-positive vs. HIV-negative groups

| Treatment | HIV-positive patients | HIV-negative patients |
|---|---|---|
| | N (%) | N (%) |
| Amoxicillin – clavulanic acid | 17 (94.4%) | 5 (83.3%) |
| Azithromycin | 2 (11.1%) | 1 (16.7%) |
| Vitamin A | 17 (94.4%) | 5 (83.3%) |
| Corticosteroids | 6 (33.3%) | 1 (16.7%) |

## 3.10.8 Outcomes

The HIV-positive group had a significantly (p=0.03) longer hospital stay 4 days (range 1- 31 days) compared to 1.5 days (range 1 – 4 days) in the HIV-negative group. There was however no significant difference with respect to death in the two groups (p=0.55), there were 3 deaths in the HIV-positive group and none in the HIV-negative group (Table 3.20).

Table 3.20 Outcomes: HIV-positive vs. HIV-negative groups

| | HIV-positive patients | HIV-negative patients | p |
|---|---|---|---|
| Length of hospital stay (days) | 4 (range 1- 31) | 1.5 (range 1 - 4) | 0.03 |
| Discharged, N (%) | 15 (83.3%) | 6 (100%) | 0.55 |
| Death, N (%) | 3 (16.7%) | 0 | 0.55 |

# 4.0 DISCUSSION

Study results will be discussed in this chapter. Challenges encountered as well as recommendations for clinical practice will also be made.

## 4.1. Study Population and Demographics

Over the six month period between 1 October 2009 to 31 March 2010, 51 adult patients between the ages of 16-35 years were admitted to Charlotte Maxeke Johannesburg Academic Hospital with suspected MV infection. Serological confirmation (MV IgM positive) of MV infection was available for 33 patients (64.7%). Despite having clinical features suggestive of MV infection, 12 (23.5%) patients had negative MV serology. Negative serological testing may be attributed to possible laboratory errors; patients not having mounted an adequate immune response; or undetectable antibody levels within the first 72 hours of the exanthem appearing. Those patients with positive MV serology were analysed further.

## 4.2 Past History

The MV vaccination schedule incorporating two doses of the vaccine was included into the South African EPI in 1995 (106). As part of the EPI the measles vaccine is given to the child at 9 months of age with the second dose being given 18 months. Although antibodies formed in response to the MV vaccine are considered to provide lifelong immunity, protection against MV infection may be incomplete due to a number of factors, including: break in the vaccine cold chain during handling; children only receiving one dose of the MV vaccine; and comorbid immunosuppressive states such as HIV infection which have been shown to result in lower levels of Ab production (82, 84, 107, 108). A measles ‘mop up’ mass vaccination

campaign was conducted by the South African Department of Health between 12 and 23 April 2010. This campaign was conducted in response to the recorded MV outbreak which began in March 2009 in the Gauteng province (102). The vaccination campaign was aimed at providing children between the ages of 6 months – 15 years with a single MV vaccine. The aim of a mass vaccination campaign is to reduce the severity of the outbreak by increasing the population herd immunity. In the current study measles vaccination history was only recorded in 12 of the medical records reviewed. Furthermore, history of possible measles contacts was also poorly detailed. A thorough vaccination history, exposure to possible contacts, and a past history of communicable childhood illnesses are important details to document when recording a patient's history. However, a history of measles immunisation or infection is not always reliable predictor of measles immunity (89).

## 4.3 Presenting Features

The median duration of symptoms prior to presentation in our cohort was 4 days, with a range of 1 to 7 days. Published data from adults infected during the MV outbreak in Macedonia (109) as well as in Israel (110), report a similar time from first symptom development to presentation at a medical facility. In contrast to this, French soldiers presented with symptoms after a mean period of 1.4 days (111). This shorter period from symptom development to initial presentation could possibly be attributed to ease of accessing medical care, and vigilance in detecting potential outbreak situations in a military setting. Patients in the current study presented commonly with rash and fever; this is in line with presenting symptoms reported in other case series (110, 111, 112). Although all of our patients presented with conjunctivitis, the presence of this condition varies widely from 48 - 97% in different published reports (14, 112, 113, 114).

## 4.4 Laboratory and Radiological Investigations

The radiological findings in our cohort, of bilateral pulmonary infiltrates and consolidation, are consistent with those reported in other studies of adult patients infected by/admitted with MV (14, 110, 112). Few published data document results of laboratory investigations in patients with measles infection.

## 4.5 Complications and Outcome

Measles infection was complicated by pneumonia in 36.4% of our hospitalised adult patients. This compares to a recent French case series by Stahl et al. (14) in which 156 (34%) of the 460 adults with measles presented with pneumonia. Pneumonia occurs more commonly in children than in adults infected with the MV. Data from the paediatric unit (children < 13 years) at CMJAH documented that 58/62 (94%) of the admitted children developed MV associated pneumonia during the outbreak of 2010/ 2011 (115). In our cohort, six patients (18.2%) were admitted to ICU, three of whom required mechanical ventilation and subsequently died. In the above mentioned French series, 27/460 (6%) patients were admitted to ICU, 13 were ventilated and only one died (14). A similarly low death rate (1/128) was reported in hospitalised adults with measles in Macedonia during the 2010/2011 outbreak (106), and no deaths were recorded in a 2007 Saudi Arabian study (116) of 242 patients (including 24 adults), nor in the 20 adults hospitalised during the 2007-2009 outbreak in Paris (117).

Three patients in our cohort developed acute kidney injury (AKI). These patients all had severe measles with respiratory failure requiring ICU admission and mechanical ventilation.

AKI most likely cannot be attributed directly to the MV, but was more likely due to multi-organ failure.

Pancreatitis is a relatively rare complication of measles infection; there are only a few published case reports in adult patients (118, 119, 120, 121). One patient in our series developed acute pancreatitis. The recent French study reported four patients with elevated serum amylase and lipase (14).

## 4.6 Comparison of HIV-Infected and Uninfected Patients

Our study provides data on the largest series of hospitalised adults infected with HIV and co-infected with measles. Unlike other published literature, we were also able to provide a comparison of adult patients infected and uninfected with HIV, within the same cohort.

Only patients with positive MV serology, and admitted to hospital, were included in this study. Overall 18/24 of the patients (75%) who were tested were found to be infected with HIV. Six patients (25%) were tested and found to be uninfected, and nine of the 33 admitted patients did not have an HIV test carried out. Testing for HIV infection can only be conducted with the patient's permission, which may have been associated with a refusal of testing. The incidence of HIV in this cohort is remarkably high compared to the general population prevalence of HIV infection. In 2012 the estimated adult (aged 15 – 49 years) prevalence rate of HIV/AIDS in South Africa was 18.8% (122). However, this high rate of HIV infection among our measles cases may be because HIV-infected patients are more likely to acquire measles and require hospitalisation (100) firstly because of an inferior response to measles vaccination, and secondly because HIV-induced immune deficiencies are compounded with the immune-suppressive effect of the MV (21, 22, 23, 82, 84, 85).

## 4.6.1 Demographic data

Twice as many females as males presented in the subgroup infected with HIV. This may reflect the burden of HIV infection amongst women in the South African population (122).

## 4.6.2 History, examination, and laboratory findings

Presenting symptoms, findings on clinical examination, and laboratory results revealed no significant differences between the HIV-infected and uninfected subgroups. All of the patients infected with HIV presented with features typical of MV infection, including a morbilliform rash. This contrasts with published data documenting atypical findings in HIV-infected patients (48, 76). Furthermore, this is also despite the median CD4 cell count of 109 cells/mm$^3$ in the HIV-infected subgroup, suggesting advanced retroviral disease and immunosuppression. Interesting to note is that despite the low mean CD4 cell count the HIV-infected patients had a mean serum albumin within the normal range, and higher than the HIV-uninfected subgroup (although not significantly different).

## 4.6.3 Complications and outcome

Measles is typically a self-limiting illness, but individuals who are immunocompromised are at increased risk of severe disease (46, 123). Half of the HIV-infected adults in our cohort developed complications related to MV infection, as compared to only 1 patient in the HIV-uninfected subgroup; however this was not statistically different. The length of hospital stay was significantly higher in the HIV-infected subgroup ($p=0.03$). All three deaths recorded in our cohort occurred in the HIV-infected subgroup, resulting in a case fatality rate of 16.7%. Mc Morrow et al. (100) also observed an increase in case fatality among inpatients with HIV infection, as did other published paediatric studies (104, 123). The CMJAH paediatric study,

during the measles outbreak in 2010, included 16 children infected with HIV but the 2 case fatalities were HIV-uninfected (115).

## 4.7 Potential Limitations

- This study excludes patients who were seen in the casualty department but not admitted to hospital; thus only patients with more severe disease were included and this may have biased the results.
- Only patients confirmed to have MV infection by serological testing were included in the cohort. HIV-infected patients may have deficient antibody synthesis and serological testing may therefore not be a useful method for the diagnosis of measles in this subgroup.
- This was a retrospective record review and not all records reviewed contained a complete information set.
- Our cohort consisted of a small sample size. A small cohort of HIV-infected and HIV-uninfected patients may not allow for accurate statistical analysis.
- Much of the published data on MV infection concerns paediatric population making data comparison with previously published studies difficult.
- Few data from African countries was available for comparison with our results.

## 4.8 Conclusions

This study describes the characteristics of measles infection in adult patients admitted to our hospital, with the aim of better understanding the disease profile in this group. Information

was gathered by conducting a retrospective record review of adult patients admitted with MV infection to CMJAH, during the peak of the 2009/2010 measles epidemic. Demographic, clinical, laboratory, and radiographic features of measles occurring in hospitalised adult patients were described. Outcome of patients with regards to length of hospital stay, complications, and mortality was noted; and HIV-infected and HIV-uninfected subgroups were compared.

The conclusions are summarised below:

- Patients included in this study all presented with classical signs and symptoms of typical MV infection, irrespective of HIV status.
- Complications experienced by our cohort mirror those which are well documented in medical literature.
- There was a high prevalence of HIV-positive patients in our study group, well above the South African estimated adult prevalence rate.
- HIV-positive patients had a longer hospital stay.
- The 3 case fatalities occurred in the HIV-positive subgroup.

Our findings confirm that MV is still an important cause of morbidity and mortality, even among adult patients. As there may be worse outcomes in patients with HIV infection, HIV testing should be carried out in all adults with suspected MV infection. ‘Mop-up’ vaccination campaigns should perhaps also target adults infected with HIV with the aim of attaining protective antibody levels and reducing the risk of developing disease.

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# APPENDIX A

## Data Collection Sheet

### Patient Code

### Demographic data

Age

Gender

Race

DOA

DOD

Length of hospital stay

### History

Measles contact

Previous measles

Vaccinated

Children

### Symptoms

Red eyes / oral sores

Painful ears/ ear discharge

Coryza / cough / SOB

Diarrhoea / yellow eyes

Bleeding / confusion / seizures

Other

### Examination

| | | | |
|---|---|---|---|
| Temperature | BP | HR | RR |
| Jaundice | | Conjunctivitis | Stomatitis |
| Koplik spots | | Oral thrush | LAD |
| Chest | | | Otitis media |
| CVS | | | |
| Abdomen | | | |
| CNS | | | |

## Laboratory results

| | |
|---|---|
| FBC | HIV status |
| U&E | CD4 |
| LFT | CRP |
| Measles serology | |
| Other | |

## Radiological findings

CXR

## Complications

| | |
|---|---|
| Pneumonia | Respiratory failure |
| ICU admission | Mechanical ventilation |
| Encephalitis | Seizures |
| Other | |

## Outcome

| | |
|---|---|
| Discharged | Death |

# APPENDIX B

## Ethics Clearance Certificate

**UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG**
Division of the Deputy Registrar (Research)

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**
R14/49 Dr Nina E Diana

| | |
|---|---|
| **CLEARANCE CERTIFICATE** | **M10104** |
| **PROJECT** | A Study of Measeles in Adults |
| **INVESTIGATORS** | Dr Nina E Diana. |
| **DEPARTMENT** | Department of Internal Medicine |
| **DATE CONSIDERED** | 29/01/2010 |
| **DECISION OF THE COMMITTEE*** | Approved unconditionally |

**Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.**

**DATE** 29/01/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Charles Feldman

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**DECLARATION OF INVESTIGATOR(S)**

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...