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A description of the clinical profile and case management of paediatric patients admitted with measles to the Charlotte Maxeke Johannesburg Academic Hospital

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A DESCRIPTION OF THE CLINICAL PROFILE AND CASE MANAGEMENT OF PAEDIATRIC PATIENTS ADMITTED WITH MEASLES TO THE CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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

Johannesburg, 2013

DECLARATION

I, Togara Manomano Pamacheche declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature ……

Date 30 September 2013

DEDICATION

To my wife, Patricia and my children, Rudado, Mazvita and Kudzanai for their patience and love and my mother, Winnie Pamacheche for her unwavering support.

ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral (drug)
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CHBH	Chris Hani Baragwanath Hospital
DNA PCR	DNA-based Polymerase Chain Reaction Test
DoH	Department of Health
ELISA	Enzyme-linked Immunosorbent Assay
EPI	Extended Programme on Immunization
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHR	International Health Regulations
MCIF	Measles Case Investigation Form
MCV1	Measles Containing Vaccine first dose
MCV2	Measles Containing Vaccine second dose
MDG	Millennium Development Goals
NDOH	National Department of Health
NHLS	National Health Laboratory Service
NICD	National Institute for Communicable Diseases
No.	Number
PMTCT	Prevention of mother-to-child transmission
RCCH	Red Cross Children's Hospital
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction

SA	South Africa
sd-NVP	Single-dose Nevirapine
SIA	Supplementary Immunization Activities
SMC	Suspected Measles Case
UN	United Nations
UNICEF	United Nations Children's Fund
USA	United States of America
WHA	World Health Assembly
WHO	World Health Organization

ABSTRACT

Background

South Africa experienced a major measles outbreak from 2009 to 2011. This study was done to describe the patient profile of children admitted with measles for a period during the outbreak. It includes patient demographics, clinical presentation, management and outcomes. An audit of the notification system was also performed.

Methods

A retrospective review of patient records of children admitted to the Charlotte Maxeke Johannesburg Academic Hospital as suspected measles cases or who acquired measles nosocomially was undertaken. Patient demographics and clinical information was collected using a case review form. A retrospective review of measles case investigation forms and a case-based form, with the relevant contact details of the suspected measles case (GW17/5 form) was also done in order to audit their completeness and to assess the efficiency of the notification process from the hospital to provincial and sub-district level.

Results

Sixty-nine children were admitted as suspected measles cases. However, only 62 patient's records could be retrieved (90%). The median age of participants was 7 months (IQR: 4-11 months) with children younger than 6 months of age accounting for 42% of admissions. Median duration of hospital stay was 5 days (IQR: 3-7 days). HIV exposure was noted in 33 children (53%) and of these 16 (48%) were HIV-infected. Of the 29 children with a known measles contact, 18 acquired measles nosocomially (62%). Pneumonia was the commonest reason for admission (58/62

[94%] of participants). Two children (3%) died; both were HIV exposed but were not infected, and had severe pneumonia. Evidence of previous measles vaccine receipt was established in 17/62 (27%) of patients. Fifty children (81%) were notified as suspected measles cases to the hospital infection control unit; 48 measles case investigation forms (96%) and 38 GW17/5 forms (76%) were found in the unit. Forty-five (73% of the 62 on whom a folder review was conducted) notifications were submitted to the Gauteng provincial department of communicable diseases, by the hospital, but only four (9%) of these notification forms were located in the provincial office. None of these patients had any contact tracing performed.

Conclusion

A significant proportion of measles infection affected young infants (< 6 months). HIV exposure and/or infection were an important risk factor for measles acquisition and severity. The measles surveillance system functioned poorly, both in terms of completion of relevant forms, and the chain of notification and community follow-up.

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Chapter 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Background

In South Africa (SA), a major measles outbreak occurred from 2009 to 2011. In March 2009 in the district of Tshwane, Gauteng province, a cluster of 10 suspected measles cases were initially reported.(1) Thereafter measles cases rapidly spread to other districts in Gauteng; then to other provinces with a cumulative total of 18 359 cases countrywide reported to the National Institute of Communicable Diseases (NICD) by 5 January 2011 .(2)

Gauteng province was the worst affected. According to NICD statistics the largest number of laboratory confirmed cases occurred in children aged between 6-11 months. (2) In Gauteng the worst hit district was Tshwane followed by Johannesburg. (3) Prior to this outbreak the fight against measles in SA was considered to be a success with a drop in laboratory confirmed measles cases as well as a decline in mortality. This phenomenon was occurring not only in SA but worldwide. (4) Outbreaks such as this one have made measles a disease of public health concern in SA once again.

This study was done during the 2009-2011 outbreaks. It was prompted by a concern of the number of infants aged less than 6 months presenting to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) with measles. Infants are expected to be protected from infection with measles by maternal-derived passive immunity during the first 4-6 months. The study describes the experience of the measles epidemic at

CMJAH for the period June 2010 to 31 May 2011. As part of the study, an audit of the notification process at CMJAH was carried out to assess its efficiency, as one of the strategies in eliminating measles is building a strong surveillance system.

1.2 Measles burden of disease

In 2010, the World Health Organization (WHO) reported 309 000 cases of suspected measles with the estimated number of deaths in 2008 to be 164 000 globally, with 95% of deaths occurring in low income countries. (5) Measles contributes 5% of under-five mortality globally. In some developing countries, case-fatality rates for measles among young children as high as 5–6%. (6) Developed countries are not spared, as 10-30% of their measles cases are hospitalised, assuming a substantial part of the health insurance budget.

In sub-Saharan Africa measles has remained the leading cause of vaccine preventable disease mortality. However, there has been a marked decline of 86% in measles associated deaths between 2000 and 2010. (5) The WHO reported a reduction in global measles mortality, from an estimated 535 300 deaths in 2000 to 139 300 in 2010. (7)

Mortality due to measles is not the only worrying problem but its long term morbidity is of concern. Complications such as malnutrition, blindness and measles-related encephalitis have long term deleterious effects on patients who recover from measles infection. A South African study looking at these “silent effects” of measles described cases of sub-acute measles encephalitis which occurred about seven

months post measles infection. Of note was that all the patients affected were HIV positive. (8) Some complications of measles are associated with higher case fatalities and poorer outcomes. These include malnutrition or severe wasting, giant cell measles pneumonia and encephalitis.

1.3 Measles elimination strategies

The United Nations (UN) fourth Millennium Development Goal (MDG) is to reduce child mortality by two thirds from 1990 to 2015. Since measles has a high mortality and morbidity in children, a reduction in measles related deaths in the under 5 population would result in a significant increase in achieving MDG 4. (9) Therefore, measles elimination strategies were introduced by various regions in the world.

The Global Measles Mortality and Regional Elimination Strategic Plan 2001-2005 was launched with an aim to reduce the number of measles deaths by half by 2005 .(10) The regions included The Americas, Europe, and Eastern Mediterranean region. The Southern African region also adopted national measles elimination goals similar to those pioneered in Latin America. The involved countries include Botswana, Malawi, Namibia, South Africa, Swaziland and Zimbabwe. (10)

The new strategy, pioneered in the Latin Americas, had three components: “Catch up”, “Keep up “and “Follow Up“. (11) Catch up is defined as conducting a nationwide vaccination campaign targeting all children between 9 months to 14 years regardless of previous vaccination status. Keep-up is keeping routine vaccination above 90% of each birth cohort with at least a single dose of measles vaccine. Follow up is conduct

of successive nationwide immunization campaigns every 2-5 years to target children born since the last catch-up.

This elimination strategy has shown great success, with >900 million vaccines given worldwide and a 78% reduction in measles related deaths by 2008 as well as a marked decrease in measles cases. (11-12) The Americas were the first region to achieve measles elimination in 2010. The World Health Assembly (WHA) developed a 3 step strategy to assist other regions in achieving measles elimination by 2020. In order to monitor progress in all countries the strategies were firstly to agree on definitions of specific terms relating to measles such as the case definition of a suspected case or a laboratory confirmed case. The second condition was to agree on indicators of progress to elimination, and the third was developing measures of progress. (13)

In September 2011, at the 61st session of the WHO regional committee meeting, the WHO Regional Director for Africa, Dr Luis Sambo, proposed a strategy for the elimination of measles in the African Region by 2020. (14) The specific objectives of the strategy were to: reduce measles incidence in all countries; increase access to immunization services in all districts; improve coverage during all scheduled measles supplementary immunisation activities (SIAs) and outbreak response immunization activities and improve epidemiological and virological investigation of measles outbreaks in all countries.

In April 2012, the Measles Rubella Initiative launched a new Global Measles and Rubella Strategic Plan which covers the period 2012-2020. The Plan includes new

global goals for 2015 and 2020 to eliminate not only measles but rubella as well. The strategies are:

By the end of 2015

- To reduce global measles deaths by at least 95% compared with 2000 levels.
- To achieve regional measles and rubella/congenital rubella syndrome elimination goals.

By the end of 2020

- To achieve measles and rubella elimination in at least five WHO regions .(15)

1.4 Measles control in South Africa

In 1975, South Africa introduced a single dose of measles vaccine at 9 months. Measles became a notifiable disease in 1980. (16) In 1987, there was a measles outbreak with more than 20 000 cases reported, but the largest number of cases was reported in 1992 when 22 708 cases were notified. (17) Due to the outbreak the Department of Health decided to launch a strategy aimed at measles elimination.

In 1992, a second dose of measles vaccine was introduced into the vaccination schedule at 18 months of age. This was to improve the seroconversion rate after measles vaccine, from 85% after one dose measles containing vaccine (MCV1) to 95% with a second dose of measles containing vaccine (MCV2). (16) A measles elimination goal was set to eliminate measles by 2002. South Africa together with 6 other Southern African countries mimicked the successful strategy used by the Pan

American Health region. This involved setting up a vaccination campaign based on the catch-up, keep-up and follow-up strategy.

These measles elimination strategies resulted in higher measles vaccine coverage rates locally, culminating in lower numbers of laboratory confirmed measles cases. During the past decade, SA has seen a national increase in MCV1 and MCV2 coverage from 68% and 57% in 2001 to 95% and 83% in 2010, respectively. (18) SIA coverage has remained at high levels - around 90%. Substantial heterogeneity in routine measles vaccine coverage within the context of the Expanded Programme on Immunization (EPI) is present across SA districts, with rates as low as 56% in some districts and as high as 95% in others. (18)

Occurrence of SIAs was associated with a decrease in routine immunization coverage at the district level. (18) This may be because staff that were usually based at health stations and administered the routine vaccines had to be redeployed for SIAs. Furthermore after SIAs communities do not view the routine vaccines as a necessity.

1.5 Surveillance systems

In 2005, the International Health Regulations (IHR) were adopted at the 58th World Health Assembly (WHA); in June 2007, they were entered into force for most countries. In 2012, the world approached a major 5-year milestone in the IHR. These regulations are to ensure countries have the capacities to identify, investigate, assess, and respond to public health events. IHR are put in place for early recognition of outbreaks and for better and more effective response to outbreaks of disease, in essence these regulations are for surveillance systems .(19) As SA is

part of the WHA it has a responsibility to abide by the IHR. Figure 1.1 below shows the pathway suggested by the IHR regarding reporting of events. (20)

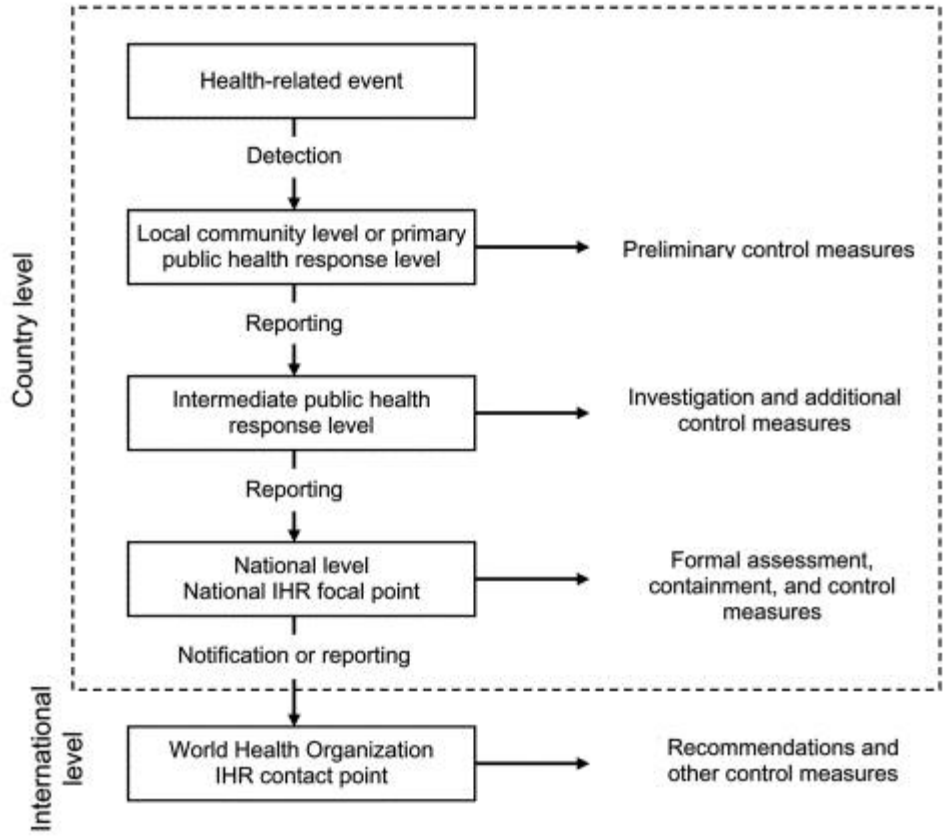


Figure 1.1: Public health surveillance structures and processes specified in International Health Regulations (IHR) 2005. Source: (20)

Good vaccination coverage has made a significant contribution in decreasing the prevalence of measles, but a good surveillance system will also contribute to measles control. A surveillance system helps identify measles outbreaks early in the epidemic, and identifies areas or populations at risk of recurrent outbreaks of measles. The surveillance statistics assist policy makers in making decisions on interventions which can effectively control measles. (21) An efficient surveillance system is one of the priorities supported by the new

WHO strategic plans as well as the African Region's committee on measles eradication.

There are different types of surveillance systems, namely, passive and active surveillance. Passive surveillance is the reporting of cases when a clinician sees a case fitting the case definition of the particular disease, whereas active surveillance is when health care workers go out and actively search for the specific cases in a defined population. Active surveillance has the advantage, in that it encourages searching for cases in populations that do not seek health care. The measles surveillance in SA is passive; therefore cases which do not present to health centres are missed. (22)

1.6 Notification process

Measles became notifiable as part of the surveillance system in SA in 1980. Notification was initially a voluntary process but in 1996 legislation was put in place (Article 108 of the Constitution of South Africa), (23) making it compulsory for medical personnel to notify every suspected measles case. This was followed by the National Health Act, Act 61 of 2003, which encompassed specific infectious diseases for notification including measles. (24)

The notification process begins with the health professional identifying a suspected measles case (SMC) as per case definition (Figure 1.2).

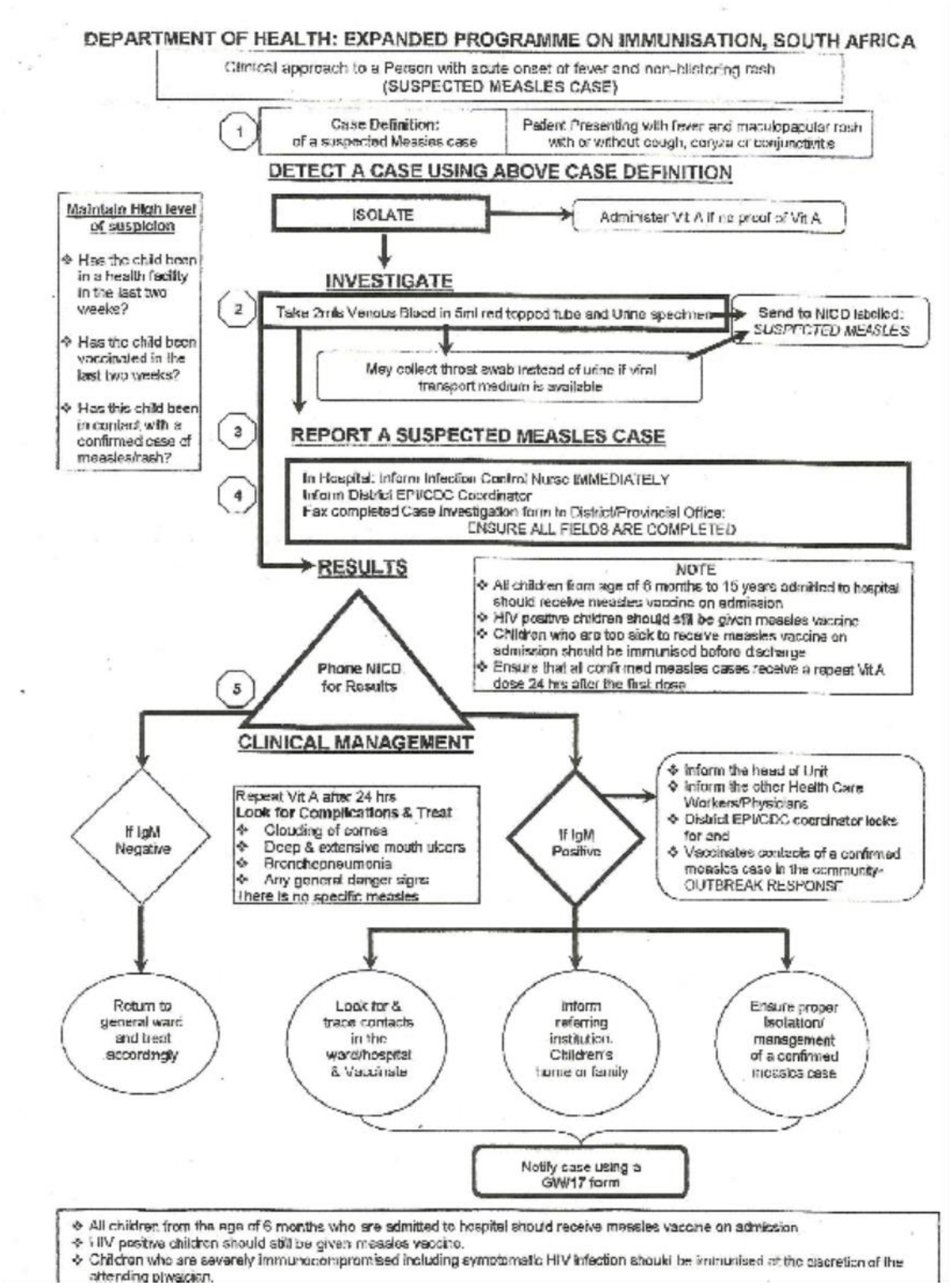


Figure 1.2 : Flow chart showing process of SMC notification and management

As a requirement a Measles Case Investigation Form (MCIF) and a notification form called GW17/5 are completed. These require relevant data about the patient including demographic data, the disease condition and actions taken by the health provider. The clinician then has to collect blood, nasopharyngeal swabs and urine from the SMC, which are sent to the National Institute for Communicable Diseases (NICD) analysis. An Enzyme–Linked Immunosorbent Assay (ELISA) for measles IgM and IgG is done on the blood specimen and a reverse transcriptase polymerase chain reaction (RT-PCR) for viral particles is done on the urine and nasopharyngeal swab. If measles virus is detected, the genotype of the virus is also determined for epidemiological mapping. (1) This is valuable in identifying whether the virus causing an outbreak is an imported virus from outside South African boarders.

The forms are then collected by an infection control nurse, who compiles a register of SMCs at the facility. The register as well as the MCIF and GW17/5 are sent to the Department of Health's regional focal person in the department of communicable diseases. The health department then distributes data to its district health officers .They identify contacts and either offer them a dose of measles vaccine, or if symptomatic refer them to a health care facility for treatment.

In the case of a death, a patient should be notified twice. Initially as a suspected case of measles on the GW17/5 form, then as a death on a GW17/4 form. For this system to be effective clinicians have to be well informed of the process and follow protocol with each case.

1.7 Reasons for outbreaks

1.7.1 Low measles vaccine coverage

According to reports by the Measles and Rubella Initiative Strategic Plan of 2012 the outbreaks in Europe and surrounding areas in 2008 were mainly due to poor immunization coverage. (25) In a country such as India accessibility to health care is a problem. This leads to low vaccine coverage rates. Studies done in rural Uttar Pradesh, India in 1996 and in an urban resettlement colony of north India in 2010 both showed that the main underlying problems leading to outbreaks were poor vaccine coverage and very poor surveillance systems leading to late detection of outbreaks. (26- 27)

Globally a decrease in funding for measles campaigns has resulted in scaling down of activities including SIAs and surveillance systems. (25) This may have contributed to the global outbreaks resulting from poor vaccine coverage as some countries are unable to procure vaccines on their own.

1.7.2 Influence of HIV infection on measles outbreaks

Sub-Saharan Africa as a region is known for its high HIV prevalence. In 2010, an estimated 22.9 million people were living with HIV in region. (27) Countries like Botswana have an HIV prevalence rate of 24% and in South Africa the prevalence of HIV is 18%. (28) There seems to be a link between areas of high HIV prevalence and recurrent measles outbreaks. The reasons for this are not clear but several studies and theories have been reported.

1.7.2.1 HIV infection and immunity

Immunity to infection in the first 4-6 months of life depends on innate as well as passive immunity. It is important that infants receive good quality as well as good titres of maternal antibodies to prevent illness during these first vulnerable months. Mothers who are HIV infected have lower titres of antibodies against measles. This is because of loss of memory B cells due to the HIV; which impairs antibody production in the mother. (29-30) Furthermore low antibody titres in mothers, translates to poor transmission of antibodies to their offspring. (31)

The low titers of antibodies result in early waning of measles antibodies before the infants are scheduled for the first measles vaccine. In a recent study, the level of measles antibodies in HIV -1-exposed babies; whether positive or negative and children who were not HIV exposed were followed from 6 weeks of age until 11 months. By 6 months of age, 91% and 83% of HIV-1-infected and HIV-1-exposed non-infected children had measles antibody levels of <50 mIU/mL which is the cut-off value for specific immune response capable of preventing infection by measles. However, 42% of HIV-1-negative children, retained high antibody levels at 6 months. (32-33)

This has therefore led to the World Health Organisation (WHO) proposing new protocols which will encourage countries to administer the MCV1 at 6 months rather than 9 months of age. This was supported by a study done in Zambia which showed good titres of antibodies on follow up. The seroconversion rate was 59% after the first dose at 6 months, then 64% seroconversion after the second dose at 9 months. (34) Though the seroconversion improved it was still lower than

The introduction of a third vaccine might not be an option for some countries in the sub- Saharan region as the cost of the vaccines seem to overburden the health systems.

1.7.2.2 HIV infection and vaccination

Infants born to HIV-1- infected mothers not only have low titres of antibodies which wane faster but they have lower seroconversion rates after vaccines. A study in 2009 showed that HIV-1 infection in Zambian children impaired the development and avidity maturation of measles virus-specific immunoglobulin G after vaccination and infection. Not only did the infants not have good responses to vaccines but even after infection their titres were low. (35)

In contrast, a Malawian study which examined measles antibody titres in mothers and children with HIV-1- infection pre and post- vaccination, comparing these to non HIV exposed or infected participants and followed them up for 24 months, showed that the participants had similar titres pre-vaccination. Both groups mounted a similar response to vaccines with similar antibody titres. However the participants who were HIV-1-infected did not have a sustained response to the vaccine but had a rapid drop in antibody titres on follow up. (36)

In a study in Zambia, measles co-infection with HIV-1-infection more than doubled the odds of death in hospitalized children. (37)

In SA, any or all of the above factors could have predisposed the population to an outbreak. The HIV prevalence is high. Secondly though the immunization coverage seems to be high, immunization coverage is calculated based on dividing the total

doses given by the target population as given by a census estimate.(16) The census estimate may have been an under- estimate based on the influx of a large number of undocumented immigrants to SA therefore theoretically lowering the vaccine coverage.

1.7.2.3 Vaccine induced immunity

In China, vaccine induced immunity to measles caused lower antibody titres in mothers compared to disease induced immunity, translating to lower titres transferred to their babies and this resulted in early waning of antibodies in infants of mothers with vaccine induced immunity. (38) A Belgian study also revealed the same result; in it 207 infants were followed up from birth over a 2 year period and also showed early waning of maternal measles antibodies in infants born to mothers with vaccine induced immunity. (39) One then can assume that with the high vaccine coverage in South Africa, it is likely that most mothers may not have come in contact with measles disease and had vaccine induced immunity, making their infants more likely to lose their antibodies earlier.

Another hypothesis is that due to the high coverage rates the incidence of measles drops. This gives communities a false sense of security and thereby encourages non-compliance to immunization of infants. These infants are protected by herd immunity and remain unimmunised, when they go on to become parents. Their offspring are then prone to measles as they do not have passive immunity and also do not have the herd immunity which their parents had from their grandparents, leading to a large population of susceptible individuals.

1.8 Justification for the study

This study was carried out in order to describe the characteristics of children with measles in SA, with a focus on children admitted with complications to a tertiary institution. A secondary objective was to compare these characteristics to other places in SA, the region as well as internationally.

It was also noticed that a large number of admissions were children aged less than 6 months in CMJAH. The study therefore sought to analyse this group and identify any characteristics that lead to this unusual age group of patients presenting with measles.

As a well-functioning surveillance system is a major contributor to measles control, the study also audited the measles case based notification system within the hospital and followed up each step through to the provincial Department of Health (DoH) and the sub-district to the index case contacts. This activity was undertaken to assess the completeness of the notification process for each patient as well to identify the strengths and weaknesses of the system.

Chapter 2: Methods

2.1 Study Objectives

Primary objective

To describe the patient profile, namely patient demographics, clinical presentation, management and outcomes of children admitted with measles.

Secondary objective

To describe the public health aspects of case management of patients, including auditing the completeness of the measles case based notification, the laboratory confirmation system and the contact tracing process.

2.2 Definition of terms

- Suspected measles case (SMC) is any individual presenting with fever (≥38°C) and a rash (maculopapular) and one or more of the following: cough coryza (runny nose) or conjunctivitis (red eyes).
- Laboratory criteria for the diagnosis of measles: presence of measles-specific IgM antibodies in blood.
- Laboratory-confirmed measles case**:** a case that meets the clinical case definition and is confirmed by the laboratory.
- HIV positive child is any child whose HIV test result is positive by either HIV PCR if less than 18 months and HIV ELISA if greater than or equal to18 months.
- An HIV exposed child: is one in whom mother's HIV ELISA is positive during that child's pregnancy.

- Eradication of measles: is a reduction of the worldwide incidence of a disease to zero as a result of deliberate efforts, obviating the necessity for further control measures. True eradication usually entails eliminating the microorganism itself, or removing it completely from nature.
- Elimination of measles refers to cessation of transmission of a disease in a single country, continent, or other limited geographic area, rather than global eradication
- Complicated Measles : a suspected measles case with any of the following, rapid breathing, some dehydration, stridor , mouth ulcers ,purulent conjunctivitis or acute otitis media with a duration less than 14 days
- The GW17/5 form is a case-based form with the relevant contact details of the SMC, to assist in contact tracing activities

2.3 Study design

This was a retrospective, descriptive study, involving a review of case records and measles case investigation forms.

2.4 Study setting

The study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This is a tertiary hospital with a paediatric unit with about 150 beds and serves as the referral centre for the north of Johannesburg. Therefore, patients seen have been referred from secondary level hospitals, clinics as well as private practitioners. It also serves about 60 000 paediatric outpatients annually.

Paediatric patients seen at CMJAH are first evaluated in paediatric casualty. After consultation, patients are admitted to the general paediatric wards.

Selby Hospital serves as a step down facility for CMJAH. In the event that there is full occupation of beds then stable patients are transferred to this facility to complete treatment.

2.5 Study sample

All children admitted to the paediatric wards with documentation indicating a diagnosis of Suspected Measles Case (SMC) over a one-year period were included in the study.

2.6 Study period

This included all patients admitted to the CMJAH paediatric wards from 1 June 2010 to 31 May 2011.

2.7 Study inclusion and exclusion criteria.

All children had to be admitted to the paediatric wards in CMJAH for study inclusion, which are wards 285 and 287. The children had to have been admitted as SMCs or to have developed measles in the wards. Because of the age restriction criteria applicable in the wards, the patients included in the study were all less than 13 years old. Neonates admitted to the neonatal wards as well as children in the paediatric haematology and oncology wards were excluded from the study.

2.8 Sample size

The sample was composed of all patients admitted over a one year period into CMJAH paediatric wards as a SMC. The period in which the sample was taken was the peak period of the national epidemic from 1 June 2010 to 31 May 2011 as shown by the NICD statistics. Due to the investigator's time constraints only one year was chosen for the study period. Based on an initial cursory review of the ward register, the sample size was anticipated to be about 100 patients but only 69 patients were identified eventually.

2.9 Data source, and study tools and procedures

2.9.1 Case records

The researcher went through the admission registers in the paediatric casualty (ward 161) and in the two general paediatric wards (wards 285 and 287). The names and hospital numbers of each case recorded in the casualty register as a SMC was identified and a list was generated. This list was kept in an electronic coded file which could only be accessed by the investigator. The researcher also went through the discharge summaries available in the discharge summary file in each ward. This was done to identify children who developed measles in the ward or were missed on admission and so would not have been listed as SMC in the admissions register

Files of SMCs identified using the strategy described above, were retrieved for data abstraction from the hospital records department. . Relevant data from the patients files was summarised into a case review record (see Appendix A). Variables compiled onto the case review record included the child's demographics details, medical history; measles contact history, immunisation status, Co-morbid illnesses, HIV status, CD4 count and antiretroviral (ARV) history, clinical findings, Laboratory test results. Each case review form was given a unique number code which corresponded to the patient's name in the electronic data base.

2.9.2 Measles Case Investigation Forms

Measles Case Investigation forms (MCIF) for the study period, were also retrieved from the infection control unit at CMJAH. Data captured in the MCIF was audited. The audit included identifying whether a form had been filled in for each study participant. This was done by checking a log-in register which lists all the MCIF collected with the corresponding wards including the date when the collection occurred. Each MCIF was searched for and retrieved. The third part of the audit was to go through each MCIF and look at all sections of the form with the intention of assessing the completeness of filling in the form. If the form was not complete the sections which were not filled in were identified and recorded in the second part of the case review record (Appendix B). Patients identified for the first time in the infectious disease records were included in the study, i.e. their hospital records were then retrieved and a case review record form completed.

2.9.3 GW17/5 Form

The South African Department of Health GW17/5 forms were retrieved using the same method as the MCIF. A relevant section was available on the case review form to audit these forms as well. (Appendix A)

2.9.4 Assessing the Notification process

Following the retrieval of the MCIF and the GW17/5 forms from the Infection control department, the next step in the audit was to follow the line of notification from the hospital to the Gauteng Department of Health (GDoH) and its branches.

Registers were retrieved from the infection control communication files. These files contained data with regard to faxes sent between the hospital's infection control department and the regional as well as the provincial department of communicable diseases. Each register contained the date the fax was sent through and the number it was sent to. Information from the hospital's fax file was also recorded onto the case review record. (Appendix A)

2.9.5 Provincial department records

Permission was obtained from the relevant department of health offices to conduct the audit within the provincial department of health as well as its branches, in order to conduct the SMC notification audit.

Records of the provincial department of communicable diseases were audited by searching through boxes of MCIFs as well as GW17/5 forms from all the districts as well as looking through the different registers faxed through from the different district health centres. Patients on the hospital list were sought from the forms found in the department of health office. When the patient's MCIFs and GW17/5 forms were retrieved further investigation into the outcome was carried out. This included checking if contact tracing was done and if it was done what the outcome of the contact tracing was.

2.9.6 Sub-district records

Focal people in each district were identified and contacted using phone numbers and emails. The list of patients was sent to the relevant sub district infectious disease focal person for information regarding the follow up of each patient. This was then recorded in the case review record. (Appendix A)

2.10 Data Processing and Statistical Analysis

Data from the case review record was entered into a Microsoft Excel 2010 (Microsoft, Seattle, USA) spreadsheet. Analysis was done using Stata 11.1 (StataCorp LP, Texas, and USA). Summary statistics were obtained for variables such as HIV status, vaccination status, and severity of illness, mortality and measles serology results. The researcher also analysed completeness of notification data. The Student t-test and chi square test were used for significance testing of continuous variables and categorical variables, respectively. A p-value <0.05 was considered as statistically significant.

2.11 Ethical considerations

Ethical approval by University of Witwatersrand Human Research Ethics committee was obtained, Clearance certificate number: M110224 (Appendix C). Permission to undertake the research project at the hospital was also obtained from the Chief Executive Officer of CMJAH. Clearance from the Ethics Committee from the Gauteng Department of Health to undertake the audit was also obtained (Appendix E).

To protect the participant's identity unique identifiers were used on the data sheets. A unique identifier was allocated to each patient's name. The patient's names were kept in a separate electronic data base which could only be accessed by the

researcher using a digital password. No names or hospital numbers were used on the data collection forms. Although these unique identifiers were used throughout most of the study, due to the nature of the study it was necessary to use the study subject's names during the audit of the notification process from the infectious disease office in CMJAH to the DoH communicable diseases as well as at the relevant districts.

2.12 Budget

The study was self-funded.

Chapter 3: Results

This chapter initially describes the demographics, clinical manifestations and laboratory data of participants. Thereafter, an analysis of the MCIF is presented, followed by a review of the notification process.

3.1 Number of study participants

For the period from 1 June 2010 to 31 May 2011, 592 patients were notified as suspected cases of measles to the infection control department, as recorded in their register in Area 421 in CMJAH (Figure 3.1). Of these 389 were children (66%) and 203 were adults (34%). However, the paediatric admission register in ward 161 (paediatric casualty) listed 428 patients as having a diagnosis of measles for the period between 1 June 2010 and 31 May 2011. Three hundred and fifty-nine participants (84%) were treated as outpatients and sixty nine were admitted to the paediatric wards (16%) for complicated measles (Figure 3.1). Of these, 62 files (90%) were available for analysis (Figure 3.1).

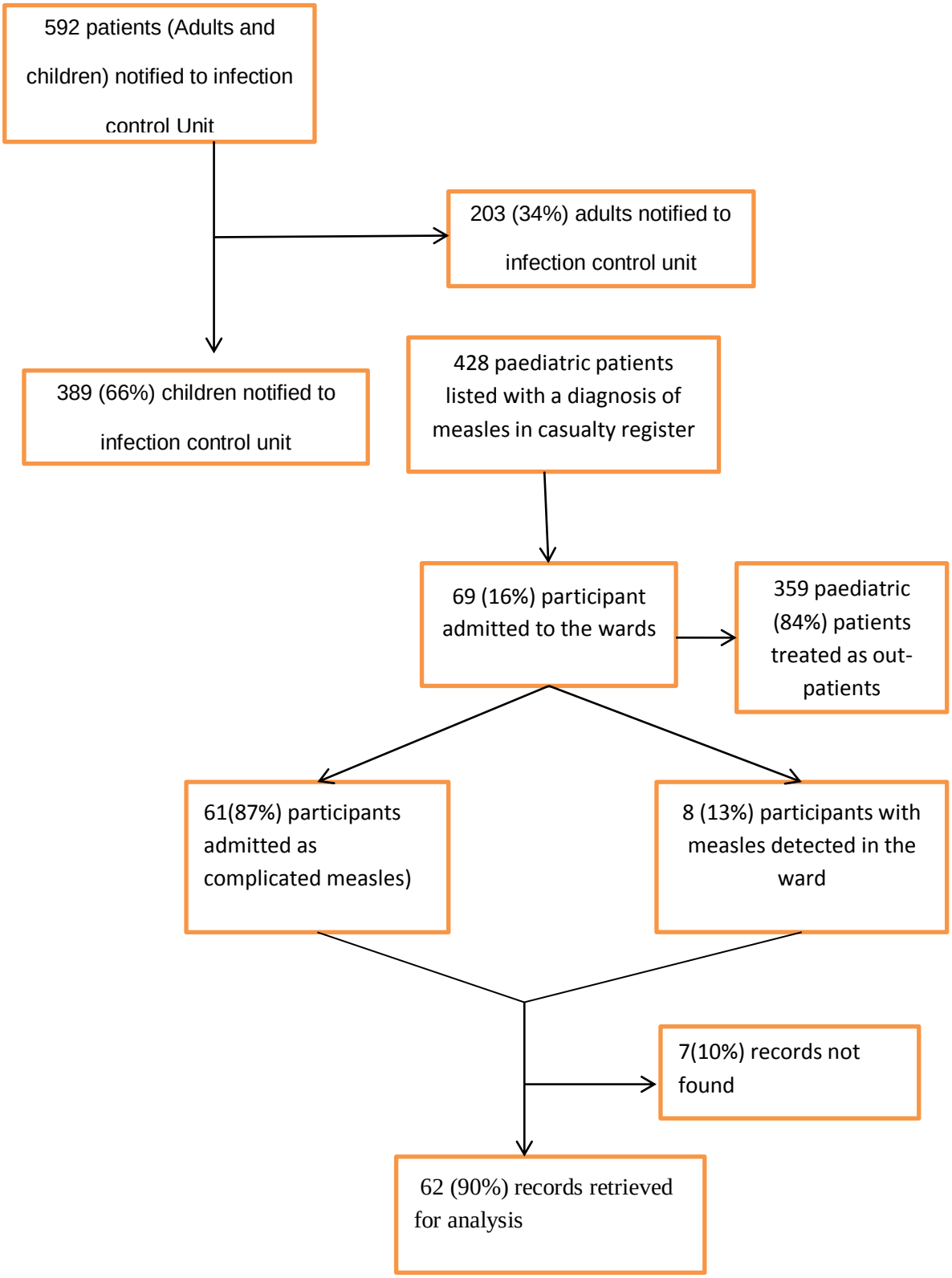


Figure 3.1 : Number of notified participants from 1 June 2010 to 31 May 2011

3.2 Demographic detail of admitted children

Sixty-two participants were included for study. Of these, 32 were male (52%) and 30 female (48%). The median age was 7 months (IQR: 4-11 months). The age distribution of participants is shown (Figure 3.2). Children less than 6 months (n=26) accounted for 42% of admissions and those less than 5 years (n=56) accounted for 90% of admissions.

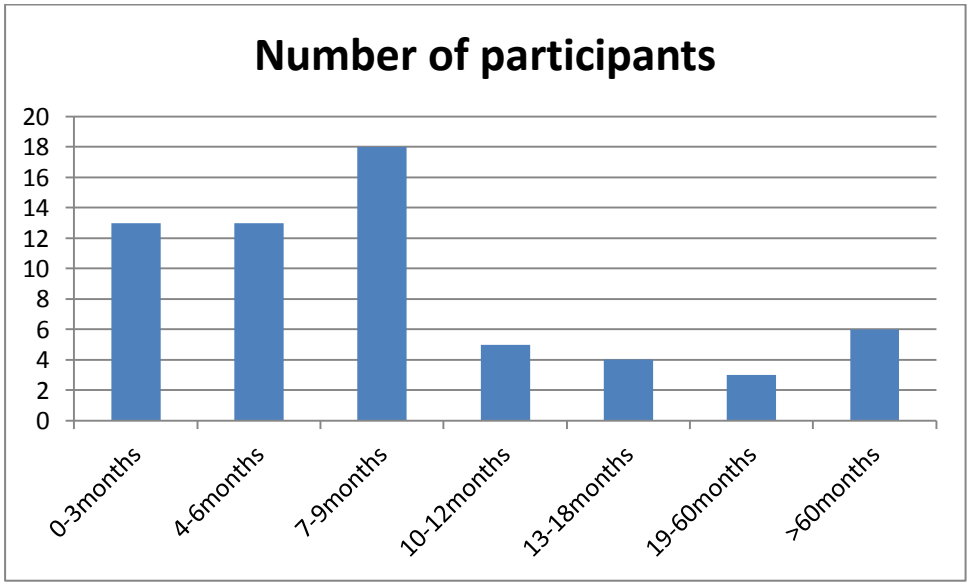


Figure 3.2: Age distribution of study participants

3.3 HIV status

3.3.1 Test status

Children less than 18 months received an HIV PCR whereas those older than 18 months got an HIV ELISA done. Of the 62 study participants, 33 (53%) were HIV

exposed. Of these, 16 were HIV positive - 13 (39%) were identified as being either HIV ELISA or PCR positive during the admission, while 3 were diagnosed previously and were on HAART , 18 (55%) tested negative, and the remaining two did not have any HIV test results recorded in the files (tests not done). Because 25 mothers (40%) tested negative for HIV during routine HIV rapid testing done to all patients on admission, 16 of the participants had no HIV test done and the nine (36%) whose tests were done were all negative. Four patients did not have any HIV exposure results documented in their files. Although three of these were already diagnosed as HIV infected and were on HAART prior to admission. It was not documented whether this was congenitally acquired HIV or acquired after birth. (Figure 3.3).

The HIV tests were positive for 16 participants; 10 (63%) were confirmed on HIV PCR testing and 6 (38%) had an HIV ELISA as a confirmatory test. Four (25%) had been diagnosed previously and 12 (75%) were diagnosed for the first time during their stay in hospital.

HIV exposure occurred in 53% (14/26) of infants less than six months of age and of these 15% were HIV infected.

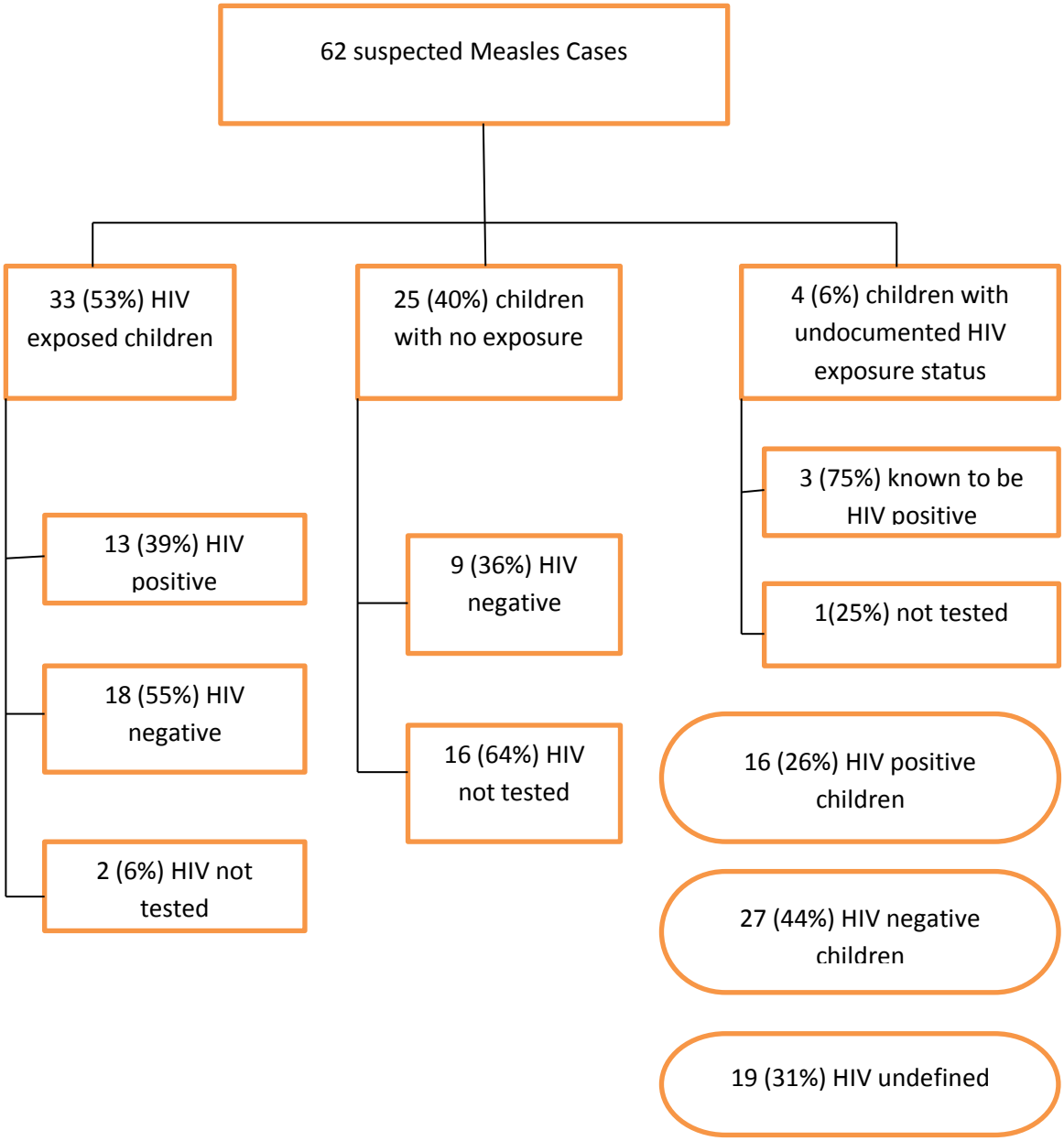


Figure 3.3: Flow of HIV status of participants

3.3.2 HIV prophylaxis

Thirty-three (53%) of the children admitted with measles were exposed to HIV in utero. Of these 18/33 (55%) had a history or record of receiving either NVP or AZT at birth as part of the prevention of mother to child transmission of HIV (PMTCT) program. Thirteen (39%) did not receive any PMTCT prophylaxis and two (6%) children did not have any record of whether prophylaxis was given.

Of the 16 HIV positive patients, five (31%) had received PMTCT prophylaxis, five (31%) did not receive prophylaxis and the other 6 (38%) had no record stating whether prophylaxis was given or not.

3.3.3 Antiretroviral treatment

Only three of the sixteen HIV infected children (19%) were on antiretroviral therapy. All three had been diagnosed prior to

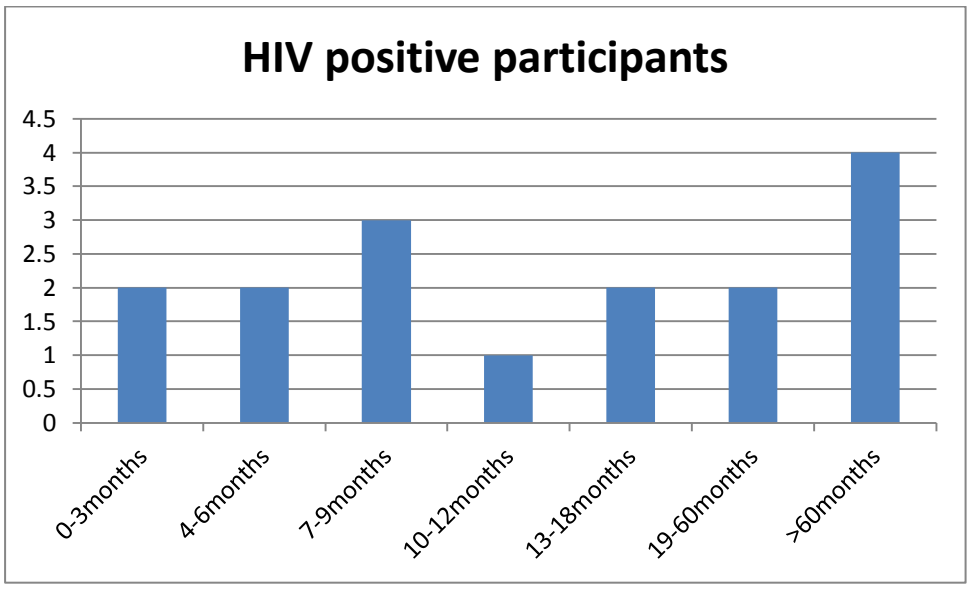


Figure 3.4: Age distribution of HIV positive participants

Of the 16 patients who were HIV positive, 4/16 (25%) of the participants (%) were aged below 6 months. Participants aged >60 months had 4/16 (25%) infected with HIV. (Figure 3.4)

3.4 Clinical features

3.4.1 Presenting features

All children were admitted for complicated measles. Fifty-nine (95%) participants presented with both a fever and a rash as per the case definition of suspected measles. All participants had a rash on admission. Additional presenting features are shown in Figure 3.5.

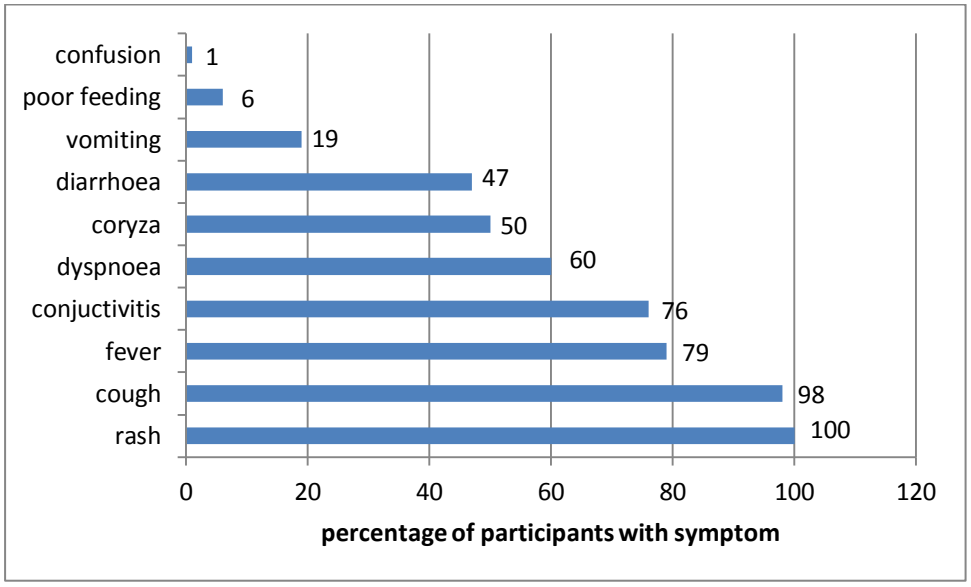


Figure 3.5: Clinical features on admission

The durations of the symptoms at the time of admission are shown in the box and whiskers plot (Figure 3.6). The median duration of all symptoms was less than 3 days.

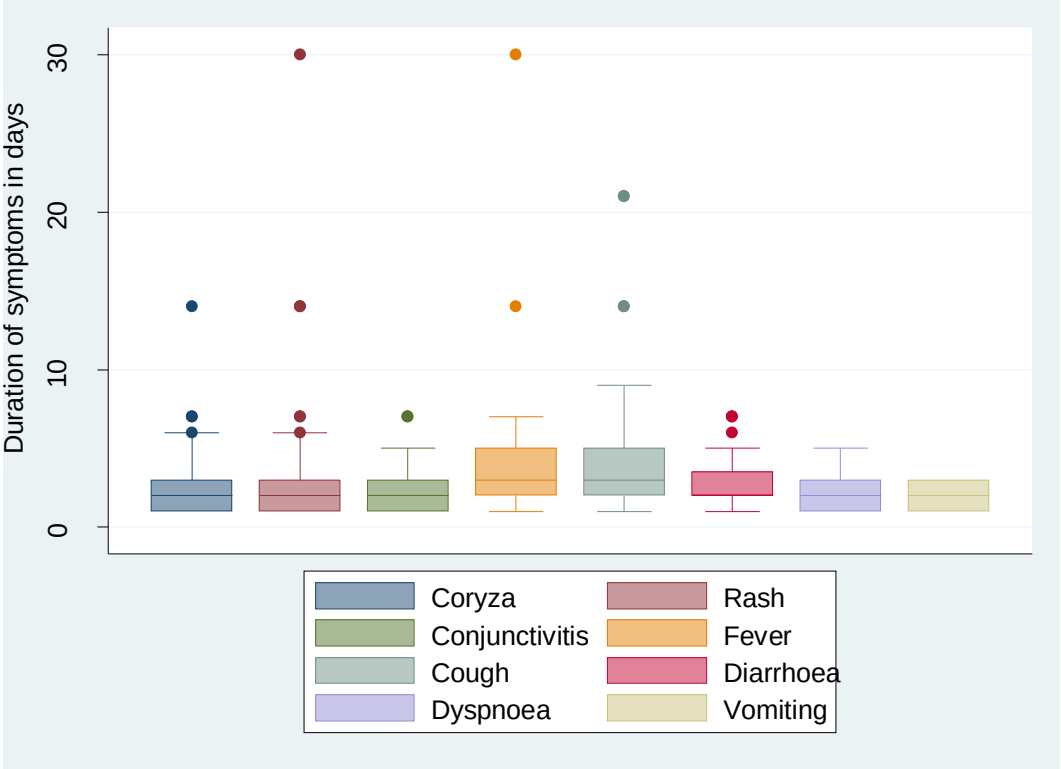


Figure 3.6: Duration of symptoms (in days) at time of admission

3.4.2 Complications

Pneumonia was a complication in 58 (94%) children. The other complications included diarrhoea (39%), laryngotracheobronchitis (17%), otitis media (4%) and encephalitis (3%) (Figure 3.7). Other less common complications included urinary tract infections, malnutrition and sepsis.

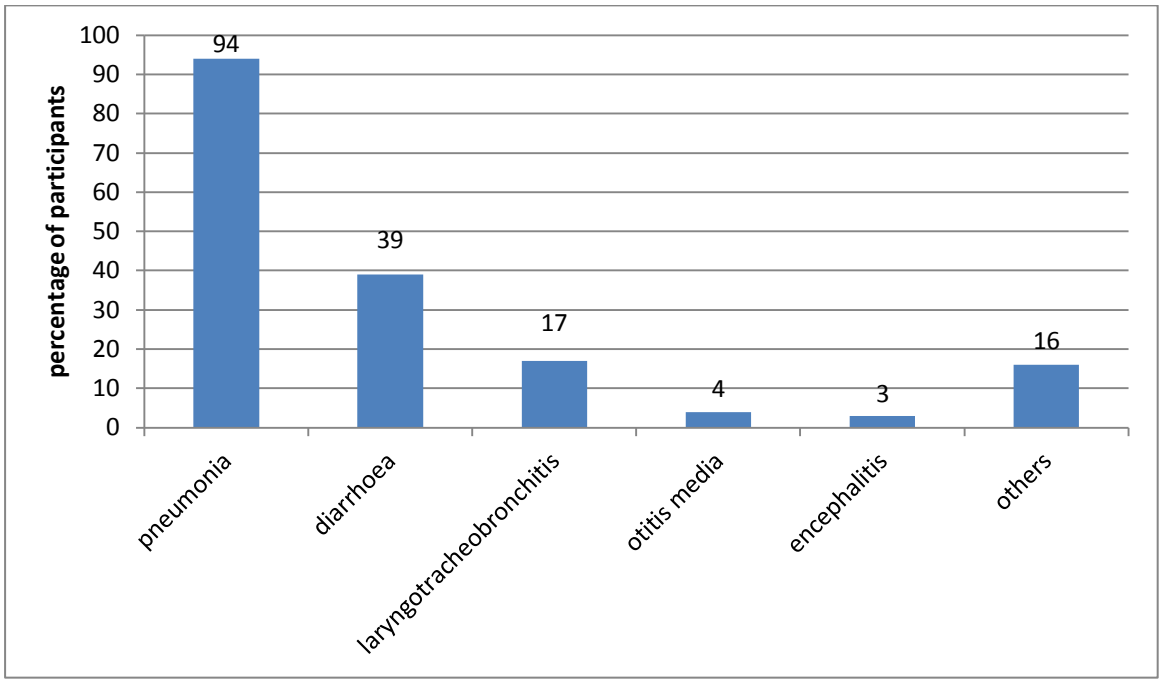


Figure 3.7: Complications occurring in participants

3.4.3 Co- morbid conditions

Children admitted for measles had other conditions. These included tuberculosis in 5(8%) of which 4 had pulmonary TB and 1 had disseminated TB.

Malnutrition was diagnosed in 9/59 participants (15%), with two thirds of the malnourished children being severely malnourished (weight-for age Z-score less than -3) the three remaining participants did not have a weight or height recorded in their files.

Urinary tract infections were diagnosed in 5(8%) of the participants. Two children had congenital cardiac defects and one child had cerebral palsy. Other co-morbid conditions included encephalitis, gastroenteritis, trisomy 21 and eczema

3.5 Outcome

Fifty-seven of the 62 participants (92%) were discharged after treatment. Three of the sixty two patients (5%) were transferred to step down facilities to create space for new admissions in the units. Their final outcome after transfer was unknown. Two children (3%) died from measles related complications.

Of the children that died, one was a 3 month old with severe pneumonia. He was admitted to the hospital for less than 24 hours. His blood cultured a coagulase negative staphylococcus (probably a contaminant). The second participant was a 9 month old who also had severe pneumonia and sepsis. His blood culture was positive for *Haemophilus influenzae*. His duration of hospitalization was 7 days. Both patients were male; HIV exposed and had negative HIV PCR tests. Their measles serologies were both positive.

3.6 Hospital stay

The duration of hospital stay was a median 5 days with an Interquartile range (IQR) of 3 to 7 days. The longest stay in hospital was 47 days.

3.7 Contact history

Thirty-four of the 62 patients (55%) had a contact history documented in the admission record; 29 (85%) of these had a known history of a measles contact. The caregivers of the remaining five (15%) did not remember if they had come in contact

with someone with measles. For 28 (45%) of the study population, no contact history was described in the admission record.

Of the 29 with recorded contact histories of measles, 18 (62%) reported to have come into contact with a person with measles at a health facility. This included clinics where children were taken for immunisation or for routine clinic growth monitoring, and previous hospitalization within 2 weeks of admission. Nine of the 29 (31%) had a history of a contact with a family member or neighbour with measles and 2 (7%) had contact in a day-care or crèche.

3.8 Measles immunisation status

Of the 62 children, 48 (77%) brought their road to health card for the consultation. Forty-five of the 62 participants (73%) had not received the MCV 1. Seventeen (27%) of the 62 children admitted for complicated measles had received a measles vaccine. Twelve (19%) had received their MCV 1 and only 5 (8%) had received both MCV1 and MCV 2 previously.

3.9 Laboratory results

Laboratory tests done on participants included full blood counts, biochemistry and blood cultures. The WHO cut offs were used to classify anaemia, thrombocytopenia and leukopenia into mild, moderate and severe. Fifty-eight patients had full blood counts on file (Table 3.1). Of these 28 (48%) were anaemic, but none had severe anaemia. Only 3 of the 58 participants were thrombocytopenic, with 8/58 (14%) of participants showing thrombophilia. Twenty patients (35%) had a leukocytosis (white blood cell count > 11 000 per cubic mm of blood).

Table 3.1 : Full blood count summary for 58 participants

Test	Number (percentage) N=58	Median	IQR
Anaemia (WHO Class.) Normal >11g/dl Mild (10-10.9g/dl) Moderate (7-9.9g/dl) Severe (0-6.9 g/dl)	 30 (52%) 14 (24%) 14 (24%) 0 (0%)	11	10-11.5
Thrombocytopenia ($x10^9$) Thrombophilia > 450 Normal (150-450) Mild (50-150) Moderate (20-50) Severe (<20)	 8 (14%) 47 (81%) 3 (5%) 0 0	304	252-414
Normal Leukopenia WCC< 4000 per cubic mm blood Leukocytosis WCC > 11000 per cubic mm blood	35 (60%) 3 (5%) 20 (35%)	9.75	6.4-12.8

Blood cultures were obtained in 45 participants; in 16 (28%) of these organisms were isolated. Coagulase negative staphylococcus accounted for 6 (38%) of the organisms cultured. The other organisms included extended spectrum beta lactamase *Klebsiella pneumonia* (4/16 [25%]), two cultures were identified as Enterococcus species, *Haemophilus influenzae* and Methicillin resistant *Staphylococcus aureus* was cultured in one participant each, and one unidentified Gram positive and one Gram negative bacillus.

3.10 Measles confirmation

No nasopharyngeal swabs were sent to the laboratory and only 19/62 urine specimens (31%) were sent to the laboratory. No test results were available for the urine specimens on the NHLS computer system.

Fifty-two participants (84%) had blood specimens sent to the laboratory for measles related investigation (Table 3.2). No tests results were found for the remaining 10 participants (16%). Ninety percent of blood specimen sent tested measles IgM positive, with 4% measles IgM negative and the remaining 6% had an equivocal result. Rubella IgM tested positive in 1/52 (2%) of the specimen sent.

Table 3.2: Measles and rubella serology for 52 participants

Test	Positive No. (%)	Negative No. (%)	Equivocal No. (%)
Measles serology - IgM	47 (90)	2 (4)	3 (6)
Rubella serology - IgM	1 (2)	50 (96)	1 (2)

3.11 Hospital management

All patients were commenced on antibiotics. Ampicillin and gentamicin were prescribed in 50/62 (82%) and 45/62 (74%) of children respectively. Other antibiotics used were; tazocin and amikacin in 9/62 (14%) of participants and meropenem and vancomycin in 3/62 (5%) participants as well as cefotaxime. Oral antibiotics prescribed were amoxicillin, cloxacillin and metronidazole. Co-trimoxazole was prescribed for prophylaxis in 17 patients.

Vitamin A was documented as prescribed in 51/62 (82%) of the children's files. The number of doses given varied with 25/62 children (41%) receiving one dose of Vitamin A, 16/62 (26%) received 2 doses, and 9/62(15%) and 1/62(2%) were administered 3 and 4 doses respectively. However 10/62 patients (16%) did not receive any Vitamin A.

Other drugs prescribed for participants included zinc, multivitamin, folate and ferrous sulphate.

3.12 Notification

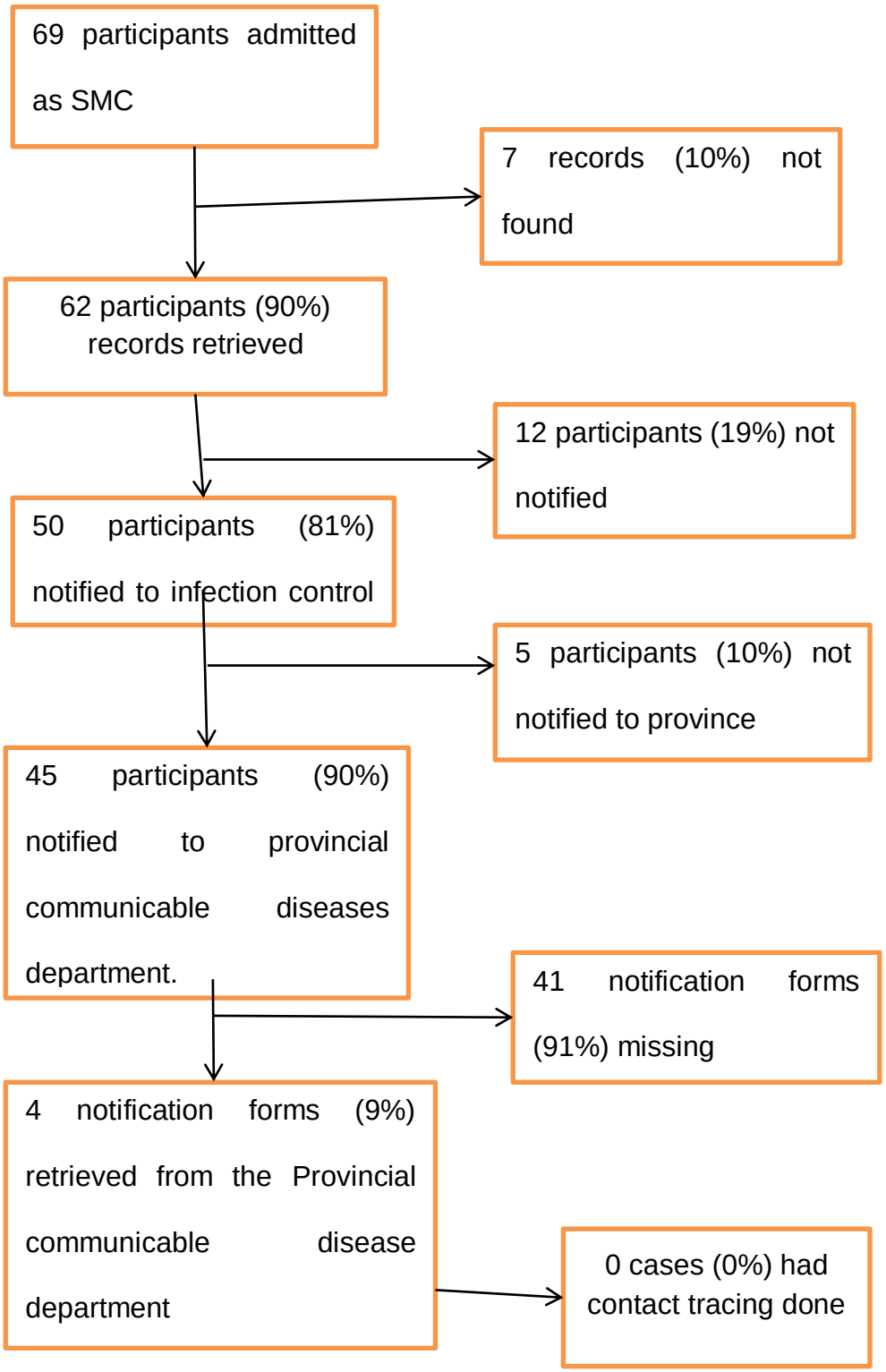


Figure 3.8: Participant notification process

Measles case investigation forms were found for 48/62 of the participants (77%) at the infection control unit, although the list of names based on the measles case investigation forms received, contained 50 names (figure 3.8).

. The audit of the completeness of the information supplied to the infection control unit, on the notification forms is shown (Table 3.3). The participant's names were filled in all the forms (100%). Ninety-eight percent of the forms had the symptoms section filled in, with the gender and address completed in 96% of the forms. The information on the specimen collected and clinical management of the participant were completed in 94% and 92% of forms respectively. Complications that the participants presented with, were completed in 88% of forms and the vaccine information was filled in 73% of cases, 56% of forms had information of the number of doses of measles containing vaccine given. Measles contact information was available in 29% of the forms.

GW17/5 forms were filled for 38/62 participants (61%). These were retrieved and analyzed for completeness

Table 3.3: Notification audit data (n=48)

Section	Adequately completed No. (%) N=48
Measles case investigation form	
Name	48 (100)
Symptoms	47(98)
Gender	46 (96)
Address	46 (96)

Specimen collected	45(94)
Clinical management	44 (92)
Complications	42(88)
Vaccine information	35(73)
Number of doses of vaccines Received	27(56)
Contact number	14(29)
Case response	0 (Not filled in)
GW17/5 filled	38(62%)

3.13 Notification process

Fifty (81%) of the 62 participant's names were on the infectious disease register, and noted as being notified. Of these 45/50 (90%) had their names sent via fax to the provincial, district and sub district health departments. Therefore 45/62 (73%) of the participants were notified to the health department.(Figure 3.10)

Sixty percent (30/50) of the GW17/5, and 64% (32/50) of the measles case investigation forms, were filled in on admission; the rest were filled in during the course of the participants stay in hospital. The time from admission to collection of the notification form was a median of 1 day (IQR 1-3 days). The duration from admission to notification of other health departments was a median of 5 days (IQR: 2-10 days) (Figure 3.9).

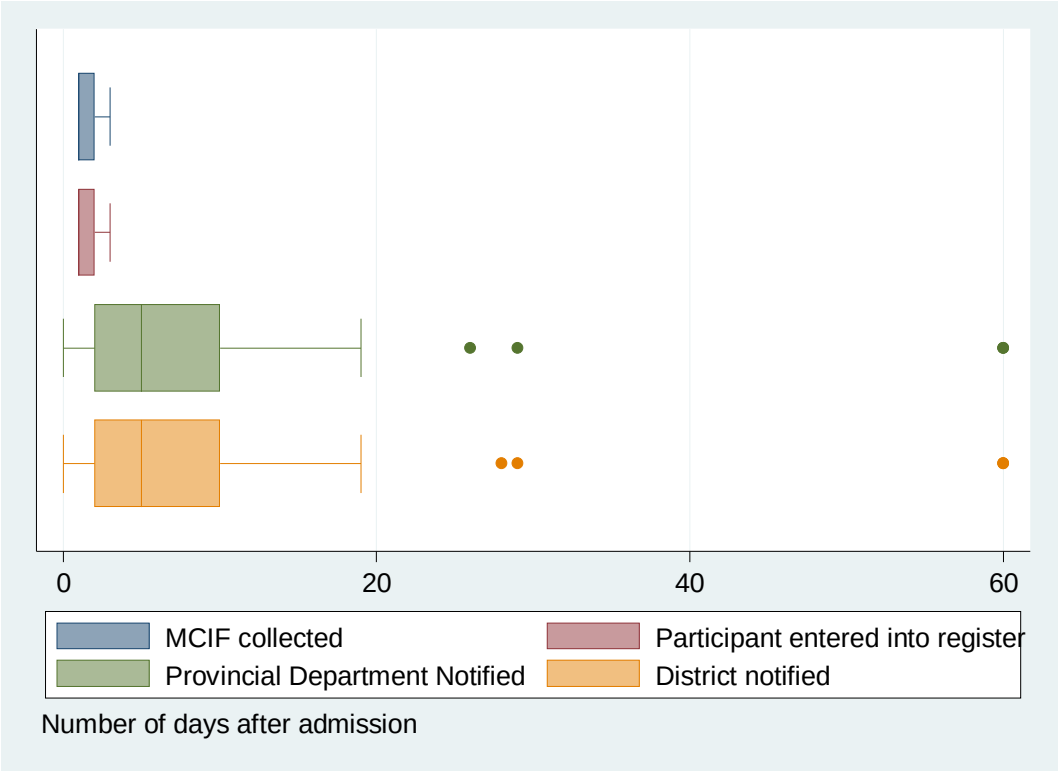


Figure 3.9: Median time from admission to notification of participants

The MCIFs were traced to the Gauteng provincial health department's communicable disease section. Only 4/45 forms (9%) were found in the Department of Health's records although a register from the faxing office at the hospital confirmed that 45 forms had been sent out to the provincial office (Figure 3.8). The investigator was informed that the forms were "lost" during recent office relocation. The outcome of the follow-up notification was not documented on any of the four forms.

3.14 Comparison between ages

The participants were divided into 2 groups by age and a comparison done between those less than 6 months old and those over. There was no significant difference using the Fischer's exact test, for complications such as pneumonia, diarrhoea, laryngotracheobronchitis and blood culture positivity amongst those aged less than 6 months and those older than 6 months (Table 3.4).

Table 3.4: Comparison of differences between participants younger and older than 6 months

	Total N	Less than 6 months	Older than 6 months	P-value
HIV exposure	33	14	19	0.52
HIV positive	16	12	4	0.12
Pneumonia	58	34	24	0.56
Diarrhoea	24	17	7	0.12
Laryngotracheobronchitis	10	5	5	0.43
Measles IgM positive	47	27	20	0.38

Chapter 4: Discussion

This chapter describes the findings in the study. The most notable finding was the high proportion of participants aged below 6 months admitted with measles. The measles surveillance system was not efficient and lacked full contact tracing to prevent further outbreaks of measles.

4.1 Early measles infection

The observation that led to this formal study was the sizeable number of children less than 6 months admitted with measles. This was unexpected as infants below 6 months acquire measles as well as other antibodies from their mothers in utero and therefore have passive immunity. This passive immunity usually wanes off between 4- 6 months. (38)

The study confirmed the veracity of this observation, with 42% of participants being in this age group this corresponds to findings in a study conducted in Cape Town during the same outbreak period.. Goodson et al. looked at the change in measles epidemiology over a ten year period and found a shift in the age of measles infections in Africa. (40) The median age of infection shifted upward to 36 months for countries with a 10 year average coverage rates of MCV1 < 50% and for countries with coverage rates between 50-74% (where in South Africa lies) the median age of measles infection shifted to 48 months.(40) This study has, however, shown the opposite.

A number of factors can be hypothesised to have resulted in the shift towards earlier measles infection in the cohort of children described in this study. The first

hypothesis was that HIV could have influenced the clinical presentation of the participants, as most of the children (53%) admitted were HIV exposed with a quarter of these being HIV positive. A Zambian study found that antibodies transmitted from mothers who are HIV infected to their infants are of poor quality and infants born to HIV positive mothers have lower titres of measles, as well as other antibodies, compared to infants born to HIV uninfected mothers.(32) This may explain why so many of the children admitted developed measles before 6 months. It has also been reported that besides the low levels of antibody titres, HIV exposed infants have a more rapid waning of antibodies making them more susceptible to infection earlier.(32) However in this study using the Fischer's exact test, there was no statistical significant difference in HIV exposure and those infected with HIV, between those below 6 months and participants older than 6 months. (P-value= 0.85 and 0.12 respectively)

A second hypothesis is that in mothers, vaccine induced immunity does not result in as high titres of antibodies as disease induced immunity.(41) The successes of the measles immunisation programmes have resulted in long inter-epidemic periods where individuals were not exposed to measles disease but only to the measles containing vaccine. These individuals may have been the mothers of the infants infected during the outbreak. Long inter-epidemic periods also result in children defaulting from receiving vaccines, as their parents do not view measles as a life threatening disease and because there is no drive by health workers as they too do not perceive the disease as a problem. These unvaccinated individuals then form a group of susceptibles who are potentially at risk of getting infected and can infect others. This may explain the large number of young infants, as well as adults who presented with measles during the outbreak.

4.2 HIV status of participants

Over 50% of the children admitted were exposed to HIV. This was higher than the national HIV exposure rate of 32% and the Gauteng infant HIV exposure rate of 30%, based on antenatal seroprevalence data.(42) Only half of the HIV exposed participants had documented evidence of receiving PMTCT which is well below the expected PMTCT coverage of 99% in Gauteng Province according to a 2010 report. (42) Some mothers tested negative during the antenatal period and only had a repeat test when their children were admitted to hospital. This resulted in 12/62 (19%) participants having their HIV diagnosis confirmed for the first time during the admission, after their mothers tests were positive. These findings highlight the short comings of the PMTCT programme and also confirm findings by Goga et al,(42) which showed that of all the women in their study 29.3% reported being HIV positive but on testing 32% were HIV positive with HIV antibodies found in 4.2% of babies born to mothers who reported to be HIV negative. This finding was attributed to mothers either falsifying reports of their test results on interview, poor testing methods at the local clinic due to poor technique when using the rapid test kits, or testing mothers during the window period and not having a follow-up test at delivery. (42)

The National HIV treatment guidelines have recently recommended commencement of Highly Active Antiretroviral Treatment (HAART) to all children below 5 years of age, but during the period of study guidelines made it compulsory to commence all infants below 12 months of age on HAART. Only 3 (19%) of the 16 participants with HIV infection were on HAART, yet 50% of them were less than 12 months (Figure

3.5 above). This was because most (12/16; 75%) of the HIV positive participants were

diagnosed during their current admission. This highlights deficiencies in HAART provision in the province, and that one consequence of being HIV positive is susceptibility to measles infection.

4.3 Vaccine failure

Vaccination should provide protection against measles infection but HIV exposed as well as HIV infected children do not seem to benefit fully from vaccination. In Thailand, the seroconversion rate in HIV uninfected but exposed children was 57% in one study after MCV1 (40), with a study in DRC showing a seroconversion rate of 76.5% compared to 85% in non-HIV exposed peers. (43) These studies support the hypothesis that the vaccine failure rate is higher amongst children exposed to HIV in utero, and to a greater extent in those infected with HIV.

Children older than 9 months admitted for measles may have had a poor response to the vaccine. As mentioned earlier in the background to this study, HIV infection in Zambian children impaired development and avidity maturation of measles virus specific immunoglobulin G after both, vaccination and infection with measles, resulting in poor responses to vaccination and low titres of antibodies after measles infection. (35)

A longitudinal study done in South Africa contradicted findings from earlier studies. It investigated vaccine specific antibody responses, comparing HIV exposed and non-exposed infants from 2 weeks to 2 years of age. It identified lower tetanus antibody

titres pre- and post- tetanus vaccination in HIV exposed infants, implying poor transmission of antibodies from mother to child and/or a poor response to the tetanus vaccine, but there was no difference in the pre-vaccination and post-vaccination measles antibody titres between the two groups.(44) These findings suggest that HIV exposed and non-exposed individuals had similar antibody titres before vaccination and had similar responses to the measles vaccine.

4.4 Admission versus outpatient management

In the current study, only 16% (69/428) of children who presented to casualty with symptoms of measles were admitted for complicated measles, contrasting with findings from Red Cross Children's Hospital (RCCH) , a tertiary institution in Cape Town, which had an admission rate of 30% (552/1861 SMCs were admitted). (45) The absolute numbers of children admitted were also significantly higher with RCCH admitting 552 SMC, during a 9 month period between 1 November 2009 and 31 July 2010 , whilst CMJAH admitted 69 over a 1 year period from 1 June 2010 to 31 May 2011. A similar study in Pakistan, Ayub Medical College admitted 136 children over a period of 2 years and 8 months from 2003 to 2005. (45-46) RCCH may have seen and admitted more patients as their study was done earlier on in the epidemic, which could have been the peak period in Cape Town.

4.5 Clinical features

Pneumonia was the most prevalent complication and reason for admission in this study. It is consistently the commonest reason for admission in children with measles. It is mentioned in different studies in Nigeria, Africa and Pakistan, Asia.(45-

48) Other complications such as diarrhoea and croup also featured in these study centres.

Individuals who are immunosuppressed are at high risk of developing severe measles, this was found in a study done on both oncology as well as HIV positive patients. (49) The study showed a greater risk of severe disease as well as a higher case fatality rate amongst patients with HIV (40%) when compared to HIV negative counterparts. Some of the patients developed complications of measles without the onset of a rash supporting the rapidity of disease progression or an atypical presentation in HIV positive children(49) There was no significant difference in symptoms between HIV exposed and HIV infected patients versus non-exposed in this study however. This may have been because the study sample was small (69), as well as if a severely ill child presented without a rash, such a patient would run the risk of not being identified as a patient with measles as the medical personnel in our institution use rash as the main clinical criteria to a diagnosis of a suspected case of measles. Education with regards to HIV patients presenting with measles without a rash will need to be done to increase awareness amongst healthcare personnel.

Of the patients who were admitted, the vast majority (93%) presented with criteria fitting the case definition of measles. Most children (79%) with symptoms which fit into the criteria for a suspected measles case were laboratory confirmed. In contrast a study showed that of all the suspected measles cases notified, between 10-20 % of them have serology confirming measles infection.(50) The high number of laboratory confirmed cases could have occurred because the study was done during an outbreak. Further, children in the study were the most ill and therefore were more likely to have true measles.

4.6 Contact history

It was interesting to note that, of the children with a contact history, most children (62%) had actually been to a health facility prior to their illness in the last 2 weeks. This may imply that they acquired the measles at a health facility consistent with a study done at Chris Hani Baragwanath Hospital (CHBH) in 1999 which traced the origin of a measles outbreak which occurred in 1999, to a child admitted to the hospital.(51) These nosocomial measles infections may have occurred because health facilities including well baby clinics have a common waiting area and do not isolate infectious patients as they arrive. This puts children at risk of infection within the health facility.

It is a requirement as stated in the department of health's EPI disease surveillance policy report, that all children less than 15 years old, who attend a health facility or are admitted to a hospital during an outbreak , receive a measles containing vaccine or if evidently immunocompromised may require immunoglobulins for prophylaxis against measles.(52) This protocol was evidently not adhered to by health care providers in the facilities these children visited.

A third of those with a contact history had come in contact with a family member or neighbour with measles. The response to family contacts should also have involved taking the child to the nearest health facility for measles vaccine as prophylaxis within 72 hours , if not symptomatic.(52) This is evidence of the lack of health education in the community of the general population. This may be because the local health clinics did not provide enough health promotion activities to inform the

community on actions to take after exposure to measles. It could also be that the department of health did not adequately use education tools such as the media in the form of television and radio adverts, to inform the population of the measles outbreak and further educate them of what to do in the event of coming in contact with an individual with measles.

Another hypothesis, evidenced in this study is that the notification process by the health department was not followed as defined by the surveillance guidelines. In this study from 45 participants notified to the provincial communicable disease department, only 4/45 (9%) measles case investigations forms were found in their possession and of these none had a contact tracing report attached to it. This implied that no contact tracing had been done, explaining why though there were known household contacts with measles, no contact tracing had been carried out to prevent further spread of the disease. It is recommended that the Provincial department of health's communicable disease department should come up with strategies to strengthen the completion of the chain in the notification process.

4.7 Deaths

The mortality rate in this study was 3%, as a result of two deaths that occurred. Mortality in measles varies depending on the region, health status of the population and resources available to manage the complications. It ranges from 0.1% in developed countries to 30% in countries with poor resources; similarly the case fatality rate was 3% in a Cape Town study during the same period. (45) A study in

Gambia showed a significantly higher case fatality (64%) amongst children less than 1 year of age.(53) In keeping with this study the deaths occurred in infants.

The cause of death in both of them was pneumonia and sepsis. This was consistent with other studies which have shown that the major cause of measles related death is pneumonia. (45,47)

4.8 Duration of hospital stay

The duration of stay of patients in hospital was similar to other centres with a median of 5 days. Studies in Pakistan and in Cape Town showed median durations between 4-5 days. (45-46)

4.9 Laboratory investigations

4.9.1 Haematological

Studies have shown that severe anaemia is associated with high mortality in children with measles. (54) None of the participants in this study had severe anaemia as defined by the WHO which is a haemoglobin level less than 6.9 g/dl. But about half had mild to moderate anaemia using the WHO classification. (55) This exceeds the population prevalence of anaemia in SA which is between 20-39%. (56)

4.9.2 Serology

The measles surveillance system demands that blood, urine and nasopharyngeal swabs be sent off to the NICD for every suspected case of measles. (1) This study found that no nasopharyngeal swabs were done on any of the patients seen. This is rather unfortunate as nasopharyngeal swabbing has been found to yield much better

results than urine or blood specimen when searching for the measles virus. Studies in Hong Kong, Australia and the Netherlands (57-59), all consistently showed that pharyngeal swabs were the better specimen for RT-PCR to detect and identify the genotype of the measles virus.

Urine is an essential part of diagnosis as it can be used for early diagnosis of measles as viral shedding in urine can be identified before serum sero-conversion occurs. It may also detect measles infection long after IgM levels have dropped, particularly in HIV infected individuals who have prolonged viral shedding after measles infection. (60) RT-PCR is the test done on the urine specimen. This identifies viral RNA and also can be used to identify the genotype of the virus, helping to identify imported virus strains.(61) Only 31% of participants had a urine specimen sent to the NICD laboratory. Lack of clinician awareness may be to blame for the poor compliance with urine collection. Clinicians seem to view blood specimen as the only test necessary for measles diagnosis and so sending off urine specimen is regarded as not necessary and time consuming as one has to attach a urine bag to infants and wait for them to pass urine. Education of the value of this specimen may improve the number of specimens sent to the laboratory.

More blood specimens (93% vs. 31% urine specimen) were collected and sent to the NICD for confirmation of measles. The results showed 90% of the specimens sent to the laboratory were positive for measles IgM. This was higher than the average case detection rate which according to an NICD report is about 1% of the total blood specimens sent in January 2011 with rubella IgM positive specimens accounting for 37% of the total. (62) This high detection rate could be due to the fact that the study was done during an outbreak and so a child presenting with a rash during that time was more likely to have measles infection.

4.10 Hospital Management

All participants admitted received antibiotics, which was appropriate as almost all of the patients were admitted with pneumonia and some other co-morbid condition. The administration of Vitamin A is a requirement in all cases of measles as it is associated with a better outcome and decreased mortality. A Cochrane review on the use of Vitamin A in measles, found that there was a decrease in mortality in those under 2 years of age if 2 doses were given and a high dose of 200 000IU was used. (63) The measles treatment protocol by the National Department of Health states that for all children with a diagnosis of SMC, Vitamin A should be given in 2 doses. The first is a stat dose on first contact with the patient and the second dose the next day.(52)

In this study 18% of the participants did not receive Vitamin A at all. Not only was Vitamin A not given when it was required, but to those who received it, 41% of the participants only got 1 dose of Vitamin A and 17% of the participants received either 3 or 4 doses of Vitamin A. The former being under dosed and the later over dosed. It can be derived from this that clinician's knowledge on Vitamin A administration in measles may need to be revisited and education given where lacking.

4.11 Notification Process

Although notification is a requirement for all suspected cases of measles, 19 %(12/62) of children did not have measles case investigation forms filled in, and 39% did not have the GW17/5 forms. The GW17/5 form (Appendix D) is a case-based form with relevant details, to assist with contact tracing, since a disease notification demands action (follow-up) at the sub-district level. It is normally filled in by health personnel. This form makes provision for the notification of cases as well as deaths. Any person contracting a notifiable disease and then dies from the disease should be notified twice: first as a case and then later as a death. (24)

Clinicians seemed to be more familiar with the MCIF than the GW17/5 form. This is supported by the higher number (81% vs. 61%) of MCIFs filled in. Only 60% and 64% of the GW17/5 and MCIF respectively were filled in on admission by the admitting clinician and so the infection control nurse had to follow up the patients and fill in the outstanding forms in retrospect leading to missed relevant information. The nurses would fill in the MCIF and leave the GW17/5 to be completed by the doctor, resulting in further missed opportunities for completion of the forms.

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The MCIF requires the clinician to fill in relevant information which is used to follow up a patient and his/her contacts and to make the process of measles surveillance and control more efficient. Of the forms filled in and handed into the infection control department at the hospital, many forms were not complete. The name was the only parameter which was consistently completed on every form but the worst done sections were on immunization history with only 73% of forms having detail on

whether the measles vaccine was received and only 56% showing how many doses of the vaccine were received by the patient. This is a relevant section as it assists the investigator to decide on whether the child had vaccine related measles or wild type measles. The information could also be used to determine if there is a high prevalence of vaccine failure if children are vaccinated but still contract measles or if there is poor adherence to the vaccine schedule leading to the measles outbreak.

The other relevant fields not completed were, participants addresses and contact numbers which are important for contact tracing. Sections on specimens collected as well as the clinical management of the patients were also not completed. As the study was a retrospective study it was not possible to interview the clinicians, to find out why certain areas were poorly filled in. This also goes back to the clinician's views on the relevance of the notification system and the lack of insight into why the forms have the relevant sections and their importance.

When the route of notification was traced, only 4 of 45 (9%) measles case investigation forms were found in the records of the Gauteng Health Department of communicable diseases. A register from the faxing office at the CMJAH office however confirmed the forms had been sent and copies of the registers were found in the department's office but efforts to trace the MCIFs were unsuccessful. On enquiry the investigator was informed that most of the notification forms had been lost. One of the reasons given by the officers in the department was that due to the outbreak, the office received a large number of forms from the various centers including CMJAH, and the office could not keep track of all the forms. Secondly there had been a recent move to new offices, and during this move MCIF were misplaced.

On review of the four available forms revealed that no contact tracing had been done for the individuals.

This suggested that the whole chain of the notification system was dysfunctional. The main aim of the surveillance system is not only to identify cases but also to trace the cases to their origin and prevent further spread of measles. The absence of contact tracing meant that there were potential measles cases in the community who were potentially able to spread the infection and perpetuate the outbreak. This could have been prevented by simply making full use of this relatively simple surveillance system.

A systematic review of notification completeness over a 35-year period in the United Kingdom showed similar results with incomplete data entries, and even for diseases under close surveillance data completeness was not significantly better. (64)Similarly, in the Pretoria Metropolitan area, notification behaviours of private practitioners found that when they encountered a patient with measles, notification was low with some clinicians reporting that they had no knowledge of the measles notification form. (22)

A study in Australia investigated the notification process amongst general practitioners and found that only about 40% of the hepatitis A and pertussis cases and 80% of measles cases had been notified by general practitioners. (59) Delays between doctor and laboratory notifications were an average of seven days for measles and some general practitioners had a poor understanding of the process of notification and most felt uncomfortable notifying an unconfirmed case. (65)

In the US, one study suggested that 85% of patients with measles sought health care and the proportion of these suspected measles cases that were reported varied from 22% to 67%. (66) Few cases were laboratory-confirmed. As in SA, the surveillance in the US is responsive to outbreaks and so reporting increased during outbreaks.

A German Hospital developed an Electronic Data Capture (EDC) system which was connected to the Hospital information system. This system would remind clinicians in the event they incompletely filled in any form including notification forms. After adopting this system, there was a highly significant improvement in completion of forms (p-value= 0.0001). (67) This approach may improve the notification system in Johannesburg but the expense of setting up such a system may be prohibitive.

4.12 Study Limitations

The study was a retrospective study and used patient's files as the main source of data collection. Information was missing from the clerking notes, as the notes reflected how much history the clinician had written. Information missing from the file could not be retrieved. Important details missing from the records included relevant histories of past illness and admissions, the immunization history including when measles vaccine was given and if the participant received Vitamin A during the clinic visits prior to measles infection. Patients feeding histories were not recorded in hospital notes. Anthropometric measurements were not written into the examination section of the clerk notes. It may be assumed that the clinician seeing the patient just

plotted them on the growth chart, but even those with recorded weights did not have heights/lengths recorded. Further, if the measurements were recorded there was often no interpretation of the measurement. The investigator could therefore not assess if there was any correlation between the nutritional status of the patient and outcomes such as death.

The caregiver's details were frequently left out of the clerking notes. This led to the unavailability of relevant information; such as whether a mother was vaccinated or if she had been infected with measles before. These missing sections may have been left out of the clerking by clinicians as they may have viewed the information as irrelevant. Some clinicians simply had poor history taking skills. Further re-enforcement of simple history taking and proper recording of notes by clinicians is recommended.

The Provincial department of communicable diseases and the infection control department in CMJAH were reluctant to have an audit done of their records and processes, mainly because of the fear that it may expose weaknesses in the system. This led to delays in getting information and access to records. Letters from the Chief Executive Officer of CMJAH and the head of the provincial department of communicable diseases assisted the investigator to gain access to the relevant records.

Most files were lost in the Gauteng Health Department of communicable disease office therefore the investigator could not adequately follow up the notification chain to the district, as there was a break in the chain. It is therefore difficult to draw any firm conclusions other than that the notification system was dysfunctional.

As measles outbreaks are influenced by climatic and geographic changes, a period of a year was chosen in order to minimize the bias arising from these influences. The geographical area could have played a major role in the number of patients seen and admitted with measles.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

- This study showed that a large number of children less than 6 months were admitted with measles. HIV might have played a role in making them susceptible to infection. It is recommended that infants exposed to HIV would benefit from an early measles containing vaccine at 6 months then follow-up vaccines at 9 months and 18 months as per normal schedule. This would improve the seroconversion rates of HIV exposed infants.
- As a large number of participants had a measles contact from a health facility, it is recommended that infants attending well baby clinics should be screened and those with a rash and fever should not be allowed to sit in the same waiting area as well babies. They should immediately be quarantined and managed. Posters should be available outside health institutions informing parents that if their child has a rash and fever, then he/she should be directed to a different waiting area from the rest and investigated. This would limit measles exposure of susceptible children.
- Enforcement of protocol is recommended. All children exposed to a measles case, whether at home or at a health facility, should receive measles containing vaccine with 72 hours of exposure.
- Health workers need periodic teaching on the importance of disease surveillance and notification. They should also be educated on how to fill in notification forms and on the relevance of each section. Periodic audits of what health care workers are doing and what problems they are facing regarding the process of notification and the information required on the

forms, should be undertaken in order to rectify problems and ensure good performance of the notification process.

- Departments involved in the notification process should have regular meetings to audit their actions and to discuss their successes and shortcomings in order to perform better.

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Appendices

Appendix A: Case record review

Appendix B: Notification form review:

Appendix C: Case Management (Public Health)

Appendix D: Ethics Clearance from University of Witwatersrand

Appendix E: Ethics clearance from Gauteng department of Health

Appendix F: Measles Case Investigation Form