Clinical characteristics and outcome of children evaluated and treated at Tygerberg Children's Hospital during a measles epidemic.

by
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Thesis presented in fulfilment of the requirements for the degree of Master of Medicine in the Faculty of Medicine at Stellenbosch University

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Co-supervisor: Dr Helena Rabie; Prof Mark Cotton

April 2014

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Declaration

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Abstract

Setting: Tertiary Paediatric Hospital, Cape Town, South Africa

Objective: To describe the clinical characteristics and outcome of children presenting to Tygerberg Children's Hospital with measles infection

Methods: This was a retrospective, descriptive study of children presenting to Tygerberg Children's Hospital, from 1 February to 31 March 2010 with a diagnosis of measles, during the measles epidemic of 2009/2010. Folders of every second admission were reviewed. Data was analysed using Statistica version 10 of 2012. The study was approved by Stellenbosch University Ethics Committee.

Results: Five hundred and eighty five children were seen and evaluated for complicated measles, 239 patients were included. Seventy nine percent (n=189/239) were admitted of which 54.3% were male. The median age at admission was 9 (Interquartile range 6 to 19) months. Children less than 9 months accounted for 50.2% (n=120) and 25.9% (n=62) were less than 6 months of age. The median WHO weight-for-age Z-score (WAZ) was 0.69 (IQR -1.82 to 0.29), malnutrition was found in 39.9% (n=81) of children less than 5 years. Children residing in the Khayelitsha sub-district accounted for 43.1% (n=103) of the study population. Uptake of the first dose of measles vaccine was 31.1% and of the second dose of measles vaccine was 23.8%. The median length of stay (LOS) was 3 days (IQR 2 – 5 days). Gastroenteritis (67.4%; n=161) and pneumonia (54.4%; n=130) were the most common complications. The majority of children had more than one complication at the time of assessment. A single dose of vitamin A was received by 71.1% (n=170/239) of children during evaluation and 47.6% (n=114/239) received 2 doses.

Seven (2.9%; n=7/239) patients required ICU care. Four (57.1%; n= 4/7) were less than 9 months of age. Pneumonia (85.7%; n=6) was the most common reason for admission.

Four (1.7%; n=4/239) children died. The median age at death was 9 months (IQR 7 – 14 months). Pneumonia (75%; n=3/4) was the most common cause of death.

HIV testing was done in 40.6% (n=97/239) of children. HIV exposure was found in 28.9% (n=69/239) on history. HIV infection was present in 8.4% (n=20/239) of children, of these, 60% (n=12/20) were on HAART. HIV-infected children were older than HIV-uninfected children (median 40 and 9 months respectively, p=0.003). Thirty percent (n=6/20) of HIV-infected children had received any measles vaccination prior to admission. Five percent (n=1/20) of HIV-infected children died vs 4.2% (n=3/72) of children who were confirmed HIV negative.

Conclusion: Our study showed that measles causes a significant burden of morbidity and mortality in children. HIV infection however did not increase the morbidity and mortality due to measles co-infection.

Interventions to improve vaccination rates and practices at community level are required in order to prevent further epidemics in the future. Further research is needed to determine whether the first measles vaccine dose should be given earlier rather than 9 months of age in order to prevent early infection.

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Abstrak

Instelling: Tersiere pediatriese hospitaal, Kaapstad, Suid-Afrika.

Objektief: Beskrywing van kliniese eienskappe en uitkoms van kinders wat aan Tygerberg Kinderhospitaal presenteer het, met masels infeksie.

Metodiek: Hierdie was ‘n retrospektiewe, beskrywende studie van kinders wat aan Tygerberg Kinderhospitaal presenteer het met ‘n diagnose van masels vanaf 1 Februarie tot 31 Maart 2010. Dit vind plaas gedurende die 2009/2010 masels epidemie. Leers van elke tweede opname is gebruik. Data is geanaliseer met Statistica weergawe 10 van 2012. Die studie is goedgekeur deur die Stellenbosch Universiteit Etiese Kommittee.

Resultate: Vyf honderd vyf en tagtig kinders is gesien en evalueer vir gekompliseerde masels, 239 pasiente is in die studie ingesluit. Nege en sewentig persent (n=189/239) is opgeneem waarvan 54.3% manlik was. Die mediaan ouderdom met opname was 9 (Interkwartielvariasiewydte 6 tot 19) maande. Kinders jonger as 9 maande het 50.2% (n=120) van die studiepopulasie verteenwoordig. Die mediaan Wereld Gesondheids Organisasie gewig-vir-ouderdom was 0.69 (IKR -1.82 tot 0.29), wanvoeding is gevind in 39.9% (n=81) van kinders onder 5 jaar ouderdom. Kinders woonagtig in Khayelitsha woongebied het 43.1% (n=103) van die studiepopulasie verteenwoordig. Opname van die eerste masels entstof dosis was 31.1% en van die tweede dosis was 23.8%. Die mediaan duur van opname (DVO) was 3 dae (IKR 2 – 5 dae). Gastro-enteritis (67.4%; n=161) en pneumonie (54.4%; n=130) was die mees algemene komplikasies. Die meerderheid van kinders het meer as een komplilkasie gehad ten tye van hul evaluasie. ‘n Enkele dosis vitamien A is ontvang deur 71.1% (n=170/239) van kinders gedurende evaluasie en 47.6% (n=114/239) het 2 dosisse ontvang. Kinders wat ‘n enkele dosis vitamien A ontvang het, het ‘n korter DVO gehad as kinders wie geen (mediaan 2 vs 5 dae, p=<0.001) of twee dosisse van vitamien A (mediaan 2 vs 3 days, p=<0.001) ontvang het.

Sewe (2.9%; n=7/239) kinders het intensiewe sorg benodig. Vier (57.1%; n= 4/7) was jonger as 9 maande oud. Pneumonie (85.7%; n=6) was die mees algemene rede vir toelating.

Vier (1.7%; n=4/239) kinders het gesterf. Die mediaan ouderdom by sterfte was 9 maande (IKR 7 – 14 maande). Pneumonie (75%; n=3/4) was die mees algemene oorsaak van dood.

MIV toetse is gedoen op 40.6% (n=97/239) van kinders. ‘n Geskiedenis van MIV blootstelling is gevind in 28.9% (n=69/239) van kinders. MIV infeksie was teenwoordig in 8.4% (n=20/239) van kinders, van hierdie was 60% (n=12/20) op HAART. MIV positiewe kinders was ouer as MIV negatiewe kinders (mediaan 40 en 9 maande, p=0.003). Dertig persent (n=6/20) van MIV positiewe kinders het ‘n masels inenting ontvang voor opname. Vyf persent (n=1/20) van MIV positiewe kinders het gesterf, teenoor 4.2% (n=3/72) van kinders wat MIV negatief bevestig was.

Gevolgtrekking: Ons studie wys dat masels noemenswaardige morbiditeit en mortaliteit in kinders veroorsaak. MIV infeksie het egter nie die morbiditeit en mortaliteit verhoog as gevolg van masels ko-infeksie nie.

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Ingryping om inenting koers en praktyke op ‘n gemeenskapsvlak te verbeter is nodig om uitbrake in die toekoms te vermy. Toekomstige navorsing is nodig om te bepaal of die eerste masels entstof dosis eerder vroeer as 9 maande ouderdom behoort gegee teword, om vroee infeksie te voorkom.

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My family: parents, husband and children, for all their support and patience.

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Introduction

Despite the availability of safe and effective measles vaccines, measles remains one of the major causes of death among children globally.

It is estimated that 139 300 people died of measles in 2010, of which a large proportion were children. Immunization has had a major impact on the reduction of measles related deaths. In countries deemed by the WHO to be high risk, one billion children from age 9 months to 14 years have been vaccinated against measles from 2001 to 2011. Deaths due to measles have decreased globally by 74% from 535 300 to 139 300 over this 10 year period. [1]

Twenty five thousand children die each day, the majority are concentrated in sub-Saharan Africa and South Asia (175 vs 6 per 1000 children in industrialized countries). Four percent of all child deaths are attributed to measles. The fourth Millennium Development Goal is to reduce the under-five mortality rate by two thirds from 1990 to 2015. [1] One of the strategies to decrease child mortality is effective control of measles infection by increasing vaccination coverage.

The current South African Expanded Programme of Immunization protocol as of April 2009 is to give the first measles vaccine at 9 months of age with a second dose at 18 months of age.[2,3] Primary vaccine failure is said to be less than 5% in immunocompetent patients. [4]

Parallel to the 2010 measles epidemic is the HIV epidemic. A number of studies [5, 6, 7] have looked at the relationship between HIV and measles regarding risk, co-infection, morbidity and mortality. Aurpibul et al showed that the main factor correlating with risk of acquiring measles infection was immunization status and not HIV infection status. [5] Scott et al concluded that infants born to HIV-1-infected women are less likely to have passively acquired antibodies to measles and therefore have increased risk of measles prior to the age of routine vaccination. [6] Moss et al concluded that rate of hospitalization, serious complication and death were significantly increased in HIV-infected infants who contracted measles, co-infection more than doubled the risk of death in hospitalized patients. [7]

Recently a number of measles outbreaks have been described globally, notably in first world countries including Germany, Italy, Switzerland, the Netherlands and Ireland. These studies showed that the majority of cases occurred in unvaccinated children, median age of 9-11 years with pneumonia being the most common complication. [8 – 12]

On 1 September 2009 the South African Department of Health (DoH) published a document to alert the public and health workers on the measles outbreak in Gauteng. In an effort to contain the outbreak, the Tshwane district embarked on a mass measles immunization campaign from 24 August to 4 September 2009. [13, 14]

On 16 October 2009 the Deputy Minister of Health invested in an urgent expert meeting where the extent of the measles outbreak and its intervention strategy were reviewed. At this stage the DoH agreed that the outbreak was localized and was planning a national mass measles and polio vaccination campaign for the first quarter of 2010. [15, 16]

On 25 February 2010 measles was officially declared as an outbreak in the Western Cape. On 22 February 2010, 422 confirmed measles cases had been reported in the Western Cape, with an additional number of serologically unconfirmed cases. [17]

On the 1st of March 2010 the Tygerberg Children's Hospital (paediatric bed capacity 310) opened a 30 bed measles isolation ward which was later increased to 35 beds due to the high number of children requiring admission for complicated measles infection. On 18 March 2010 the National Ministry of Health issued a document regarding the state of the measles outbreak in the country. To that date there had been an excess of 8615 laboratory confirmed measles cases since March of 2009. The DoH planned a countrywide mass vaccination campaign against measles and polio from 12 to 23 April 2010 in an attempt to reach at least 95% of 6 month to 14 year olds. [18]

The aim of this study was to describe the patient characteristics of children presenting to a tertiary referral hospital during the measles epidemic of 2010.

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Methods

Study design: This was a retrospective, descriptive study of children presenting to Tygerberg Children's Hospital over the 2 month period from 1 February to 31 March during the measles outbreak that occurred in South Africa in 2009/2010.

Study population: All children from 0 to 13 years who presented to Tygerberg Hospital, a secondary and tertiary referral hospital in Cape Town serving the Metro East district, and were diagnosed with measles, as per the World Health Organisation (WHO) clinical case definition (fever, maculopapular rash and cough, coryza or conjunctivitis) [(19)], during the period 1 February 2010 to 31 March 2010 were included. This study period represents the first 2 months of the measles outbreak as experienced in the Western Cape Province of South Africa.

Data collection: Ward admission books, notifiable diseases registers and the hospital administration patient record system were used to find patients with a diagnosis of measles seen at the hospital during the study period. Each patient was assigned a research number and ordered according to date of admission. Every second number was selected to participate in the research project. Data was collected from the hospital folders of all the selected patients. Folders not found after 3 searches in the hospital records department were excluded from the study; other exclusion criteria were inadequate or missing clinical notes in folders, patients older than 13 years and admission dates outside of the study period. Data was collected for demographic details, complications and outcomes, oxygen, fluid and antibiotic usage. World Health Organization weight-for-age Z-scores (WAZ) were calculated for all children 0 to 5 years of age. Malnutrition was defined as a WAZ of equal to or below -2. [(20)] HIV results were obtained from clinical notes and cross referenced from the laboratory database. Data was entered anonymously into a data collection sheet. HIV status was classified as follows: 1. Children documented to be born of a HIV-infected mother were classified as HIV exposed. 2. HIV-infected children were those who had either a documented positive HIV DNA PCR (less than 18 months of age) or reactive HIV Elisa (if above 18 months of age). 3. HIV-uninfected had a documented negative HIV PCR between 6 weeks and 18months of age or a negative HIV Elisa at any age. Antibiotic treatment was prescribed as per local treatment protocols. For the sake of more rational data analysis antibiotics were grouped into the following categories: first line oral antibiotics (Amoxicillin), first line intravenous antibiotics (Ampicillin and/or Gentamycin), second line intravenous antibiotics (Piptaz and/or Amikacin), third line intravenous antibiotics (Meropenem and/or Vancomycin), other antibiotics (Ceftriaxone, Amoxicillin-Clavulanic acid, Cefuroxime and Cloxacillin) were also used, but in low quantities, and were therefore excluded from the analysis.

Analysis: Data was entered into an excel spreadsheet. Routine analytical methods and comparative statistical analysis were performed using Statistica version 10 of 2012. The WHO Anthro (Version 3.2.2 January 2011) was used to calculate WHO Z-scores for weight-for-age (WAZ). For continuous variables (including Z-scores) means (medians) and standard deviations were calculated as measure of location and variation. 95% confidence intervals for population means were also constructed. Comparisons of 2 categorical variables were performed by means of contingency tables and significance was assessed using Pearson's chi-square. Differences between continuous variables were analysed using the Mann-Whitney test (in the 2 category case) when data were non-normally distributed and a T-test when data were normally distributed. Comparisons of more than 3 groups were performed

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using Kruskal-Wallis tests if data were non-normally distributed and ANOVAs if data were normally distributed. A significance level of 5% was applied throughout.

Ethical considerations: The study was approved by the Stellenbosch University Ethics Committee (REF N10/04/136).

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Results

One thousand three hundred and fifty four children with measles infection were seen at Tygerberg Hospital, general and isolation wards, with measles from February to June 2010. Data was collected for a total of 239 patients.

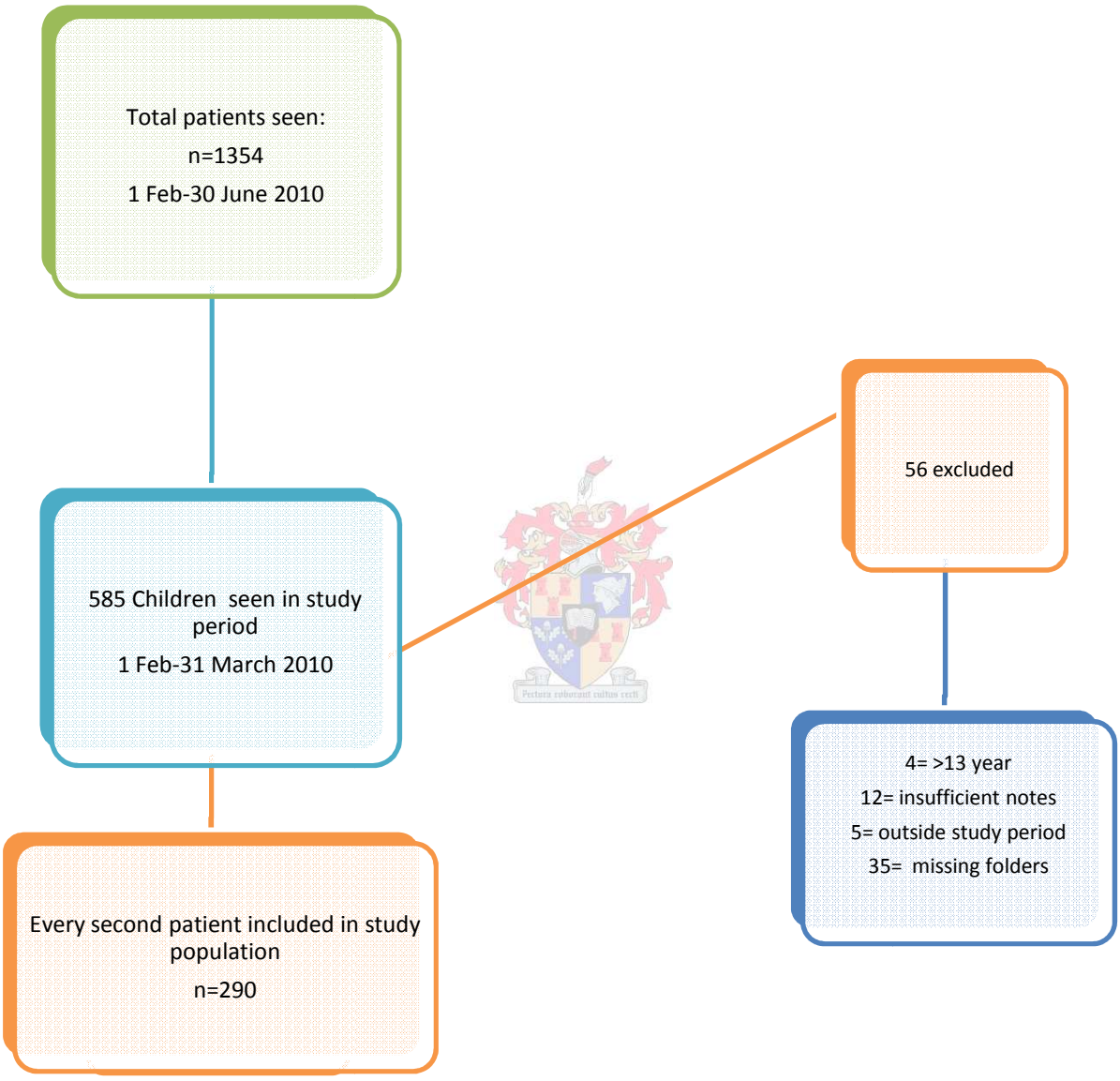

Figure 1: Selection of patients for this study from children seen at Tygerberg Children's Hospital with measles during the 2010 measles outbreak.

Male patients accounted for 54.3% (n=130). The median age at admission was 9 months (IQR 6 - 19 months). One hundred and twenty (50.2%) children were younger than 9 months old and 62 (25.9%) were younger than 6 months old at admission. Figure 2 shows the age distribution of patients.

Patients presented to hospital a median of 3 days (IQR 2 - 4) from onset of measles symptoms.

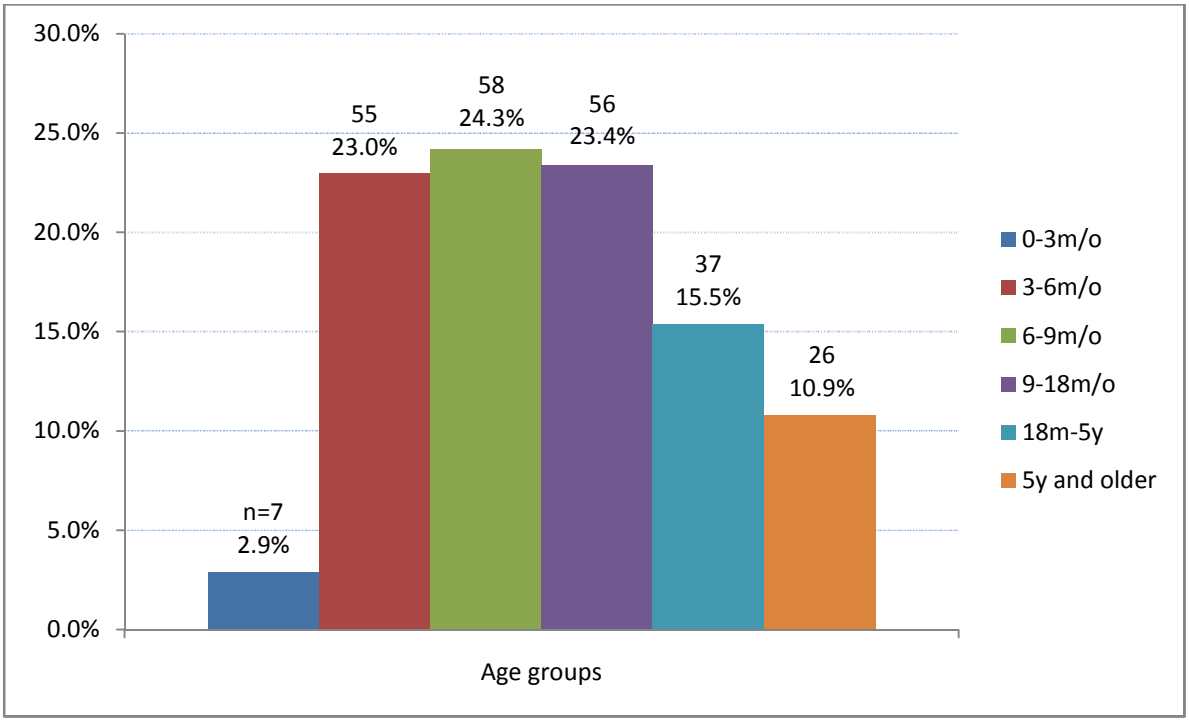

Figure 2: Age distribution of children. Subdivided into age groups and shown as percentage of total study population (n=239).

World Health Organization weight-for-age Z-scores (WAZ) were calculated for all children below 5 years of age (n=203), the median WAZ was -0.69 (IQR -1.82 - 0.29, 95% confidence interval -1.02 to -0.57). (Mean WAZ -0.8) According to WHO classification 81 (39.9%; n=81/203) were malnourished (64 (79%) underweight for age (UWFA) and 17 (21%) severely UWFA) [20].

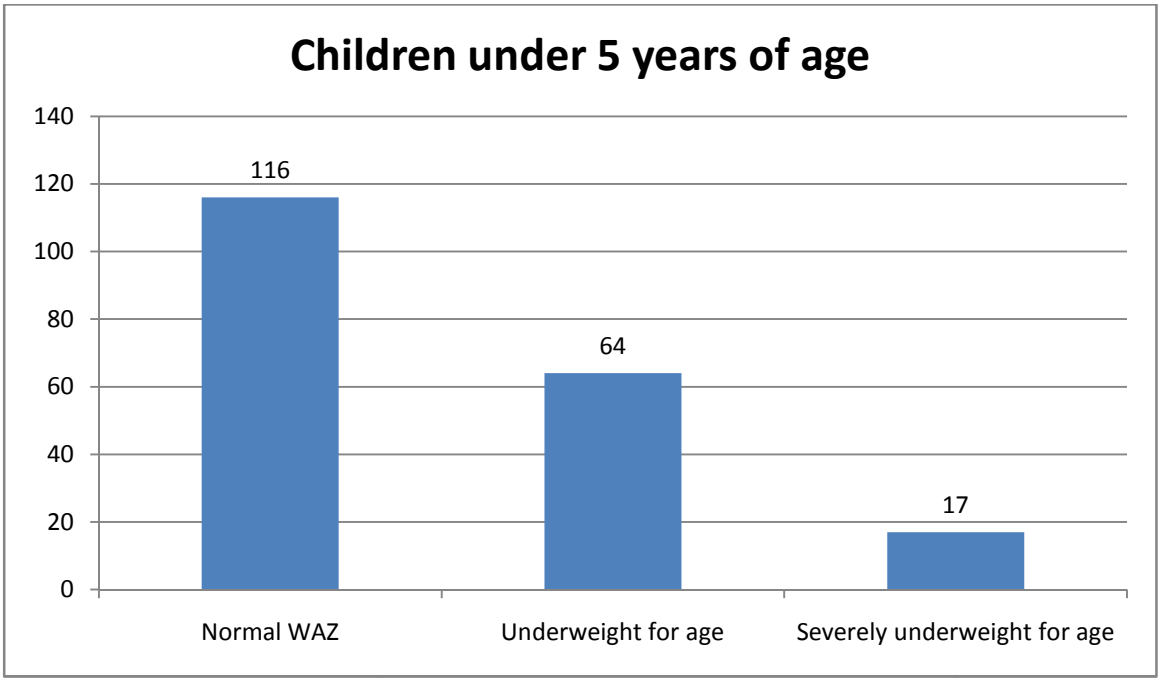

Figure 3: Weight classification for children above the age of 5 years and calculated by WHO Weight-for-age Z-score. (n=203) (6 children had WAZ above +2 and are not included in the graph.)

Geographical distribution of patients according to sub-district is shown in Figure 4.

Our study population included 103 (43.1%) children residing in the Khayelitsha subdistrict.

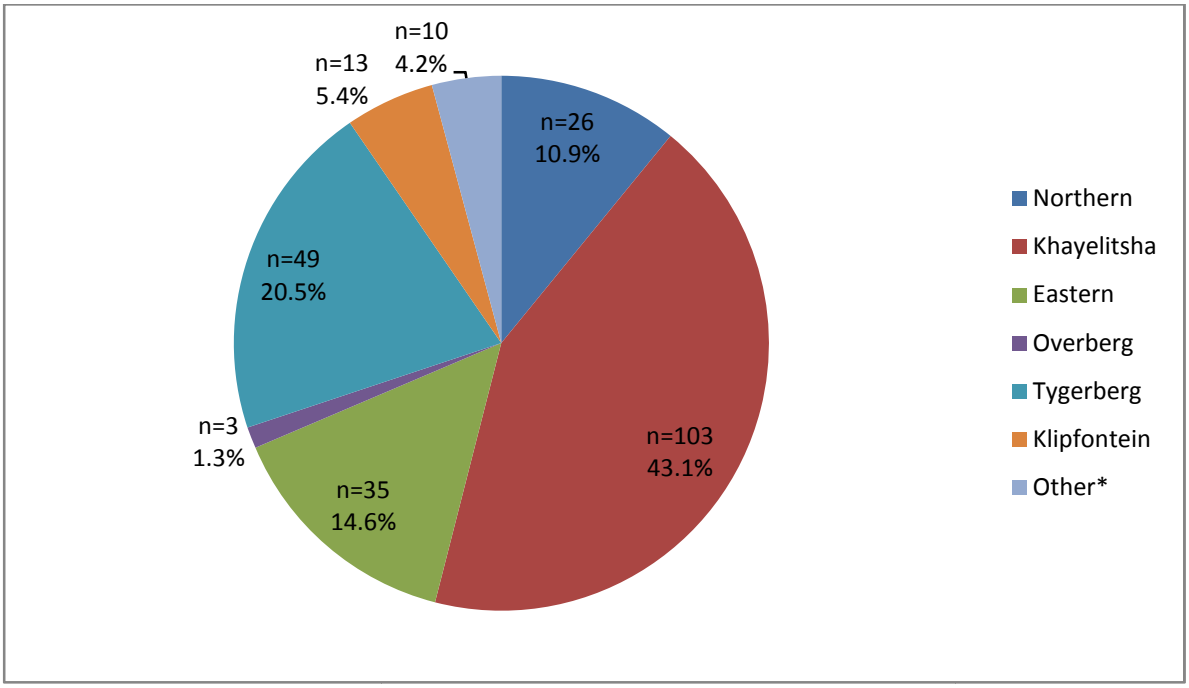

Figure 4: Geographical sub districts of residence of children, shown as percentage of total study population. (n=239) *Other: Western, Cape Winelands, Mitchells Plain, Southern district.

Vaccination status was recorded from the Road to Health cards/booklets of patients and from information gathered from the primary caregivers. Vaccination status was unknown in 25 (10.5%) children.

Uptake of the first dose of measles vaccine (9 months) was 31.1% (37/119 children > 9 months) and uptake for the second dose of measles vaccine (18 months) was 23.8% (15/63 children > 18 months).

Two children had received two doses of measles vaccine before the age of 18 months.

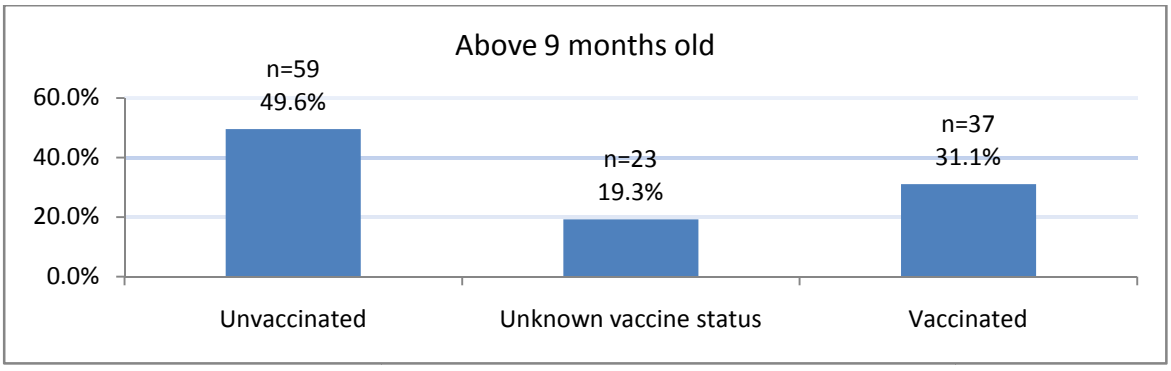

Figure 5: Prevalence of first measles vaccination (as per local EPI: 9 months of age) as percentage of children qualifying for that vaccine (ie above 9 months old) (n=119).

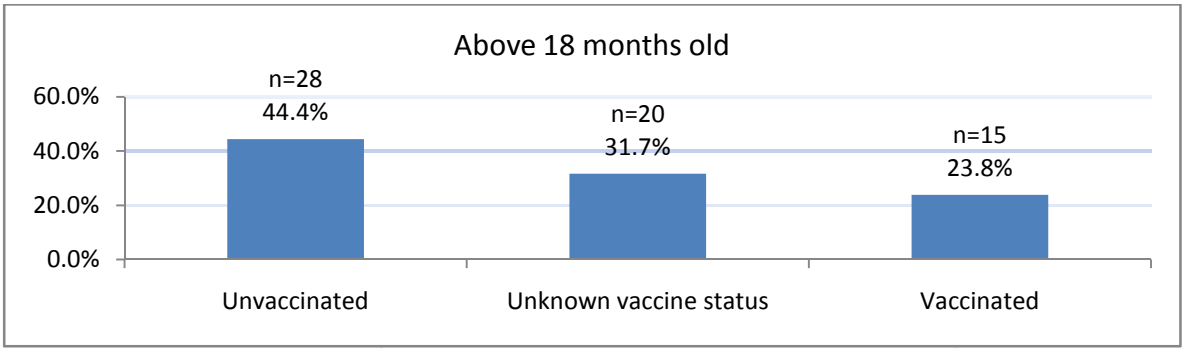

Figure 6: Prevalence of second measles vaccination (as per local EPI: 18 months of age) as percentage of children qualifying for that vaccine (ie above 18 months old) (n=63).

Of the 239 patients reviewed 189 (79.0%) were admitted. The majority, 177 (93.6%), were admitted to the measles isolation ward, of the remainder 7 (3.7%) were admitted to the short-stay ward, 3 (1.6%) to the infectious diseases ward and 2 (1.1%) directly to the paediatric intensive care unit. The median LOS was 3 days (IQR 2 – 5 days). There was no difference between age and LOS (P values for all age groups >0.05). Those < 9 months of age did not have significantly longer duration of hospitalisation (p 0.25).

There was also no difference in the median LOS across the geographic sub districts (p values for all sub districts>0.05).

The distribution of the six common complications that were enquired about on initial evaluation is shown in Figure 7. One or more complications were found in 210 (87.7%) children. Gastroenteritis (n=161, 67.4%) and pneumonia (n=130, 54.4%) were the most common. At the time of assessment 108 (45.2%) children had more than one complication. The number of complications per child is shown in Figure 8.

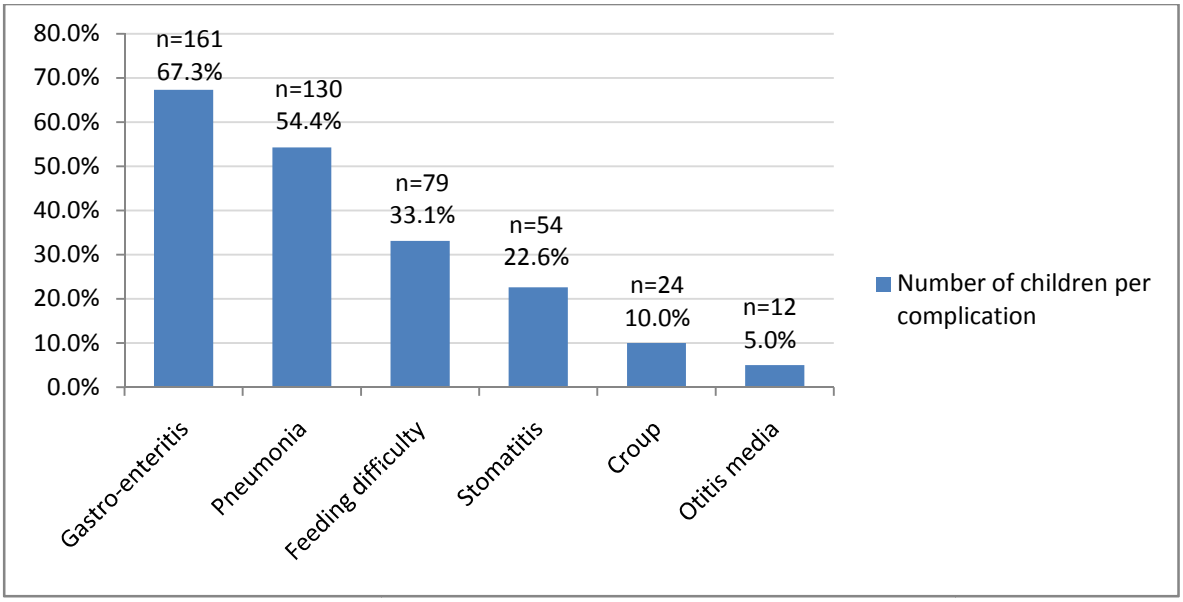

Figure 7: Complications experienced by children with measles. Complications are shown in descending order as percentage of total study population (n=239). N

indicates number of instances of particular complication, more than one complication was present per child, therefore the total number of complications were 460 (sum of n's in figure).

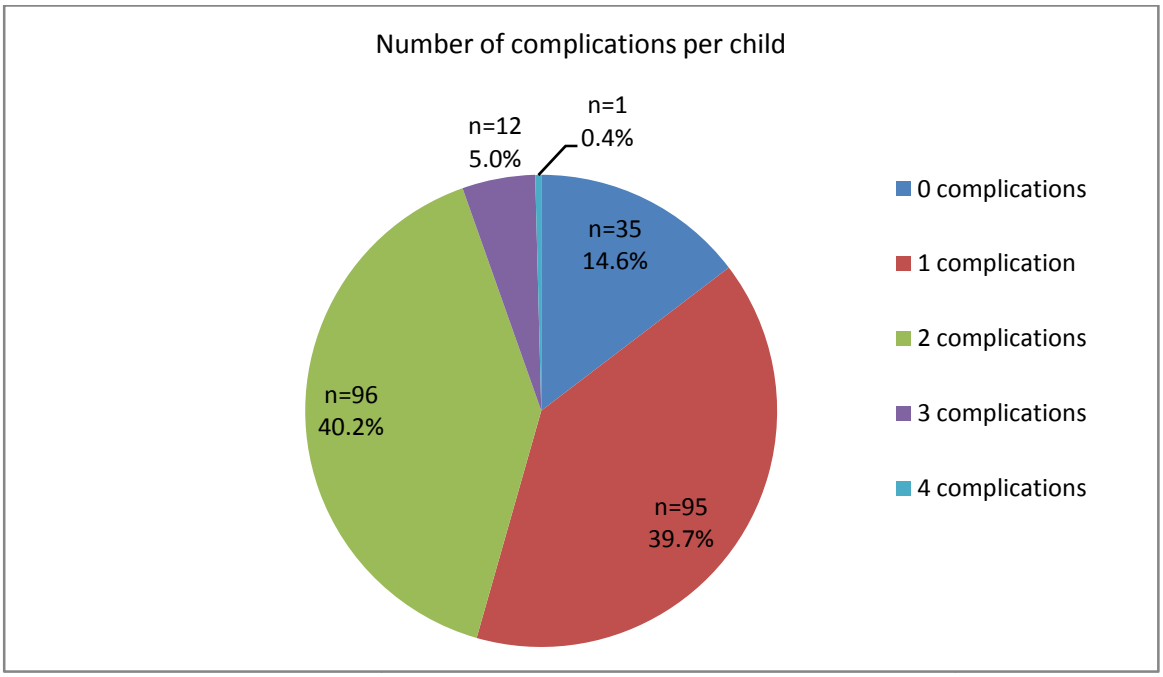

Figure 8: Prevalence of multiple complications experienced by children during their measles infection. Two hundred and four children had one or more complications during their measles infection. Percentages calculated as percentage of total study population. (n=239)

The number of complications per child in each age group is shown in figure 9. Although there was a trend that children >5 years had fewer complications than younger children, this was only significant in the 9 – 18 month age group (p=0.047).

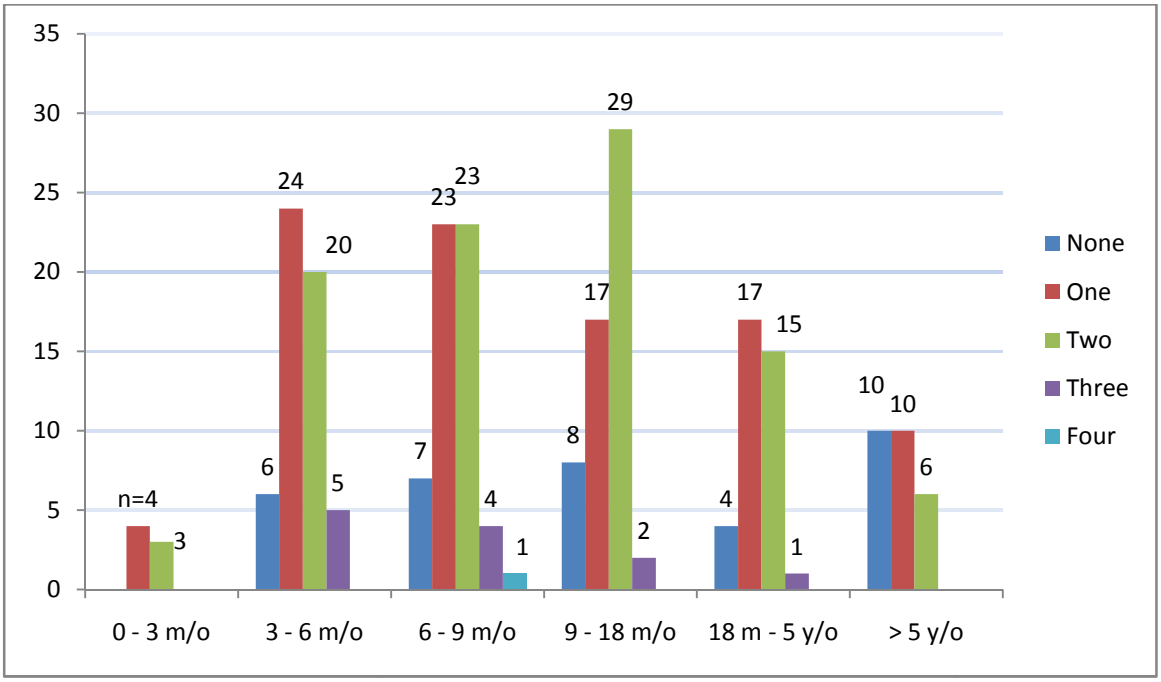

Figure 9: Number of complications experienced by children in different age categories (n=total number in each category). (total n=239)

Nasal prong oxygen was required by 64 (26.7%) children with pneumonia for a median of 3 days (IQR 2 – 5 days). Three patients required CPAP in the measles ward due to lack of available PICU beds, the median duration of CPAP support was 5 days (IQR 2 – 11 days).

Of the 161 patients with gastroenteritis, 3 (1.2%) were shocked and 84 (52.1%) had signs of dehydration. Degree of dehydration is shown in Figure 10. Intravenous fluid rehydration was required by 40 (16.7%) patients and 12 (5.0%) required nasogastric rehydration.

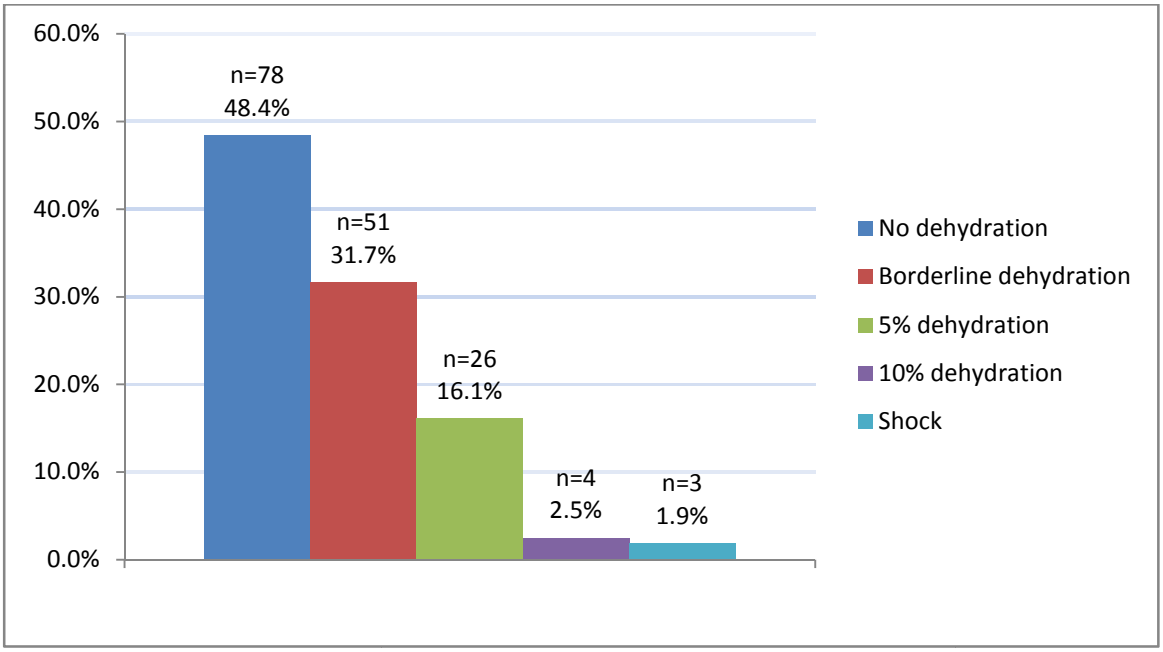

Figure 10: Hydration status of children admitted with measles and gastro-enteritis, as percentage of those who had gastro-enteritis (n=162).

Croup was diagnosed in 24 children, 20 (83.3%) required admission for adrenalin nebulisation therapy and monitoring. Children presented with croup a median of 1 day (IQR 0.5 – 1) from onset of measles symptoms vs those with pneumonia and gastroenteritis who in both groups presented to hospital a median of 3 days (IQR 2 – 4) from onset of measles symptoms.

For Vitamin A doses received at Tygerberg Hospital: 170 (71.1%) children received a single vitamin A dose while being evaluated and/or admitted to the ward and 114 (47.6%) received two doses of vitamin A during their admission. No vitamin A was received by 69 (28.9%) children during their admission to Tygerberg Hospital. We were unable to ascertain doses of Vitamin A received at clinics prior to admission.

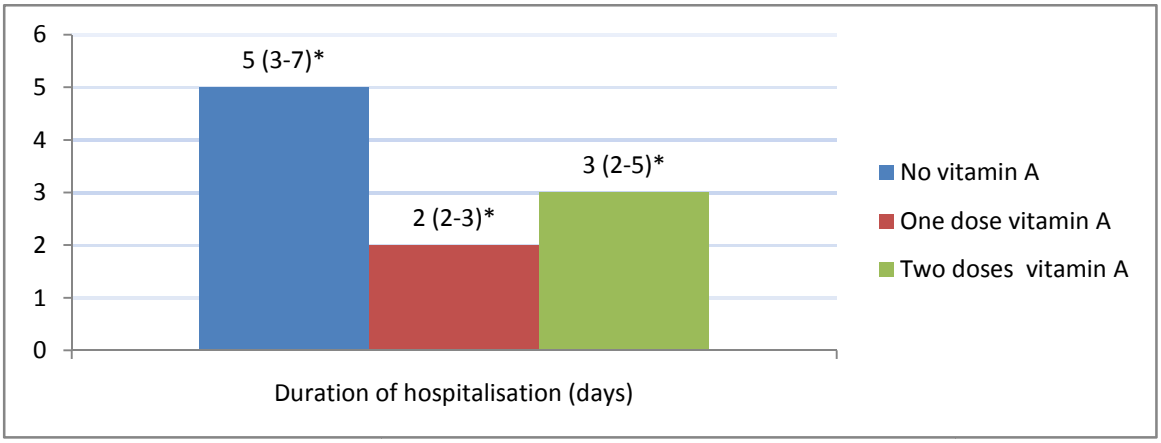

Figure 11: Duration of hospitalisation (days) of children who received no, one dose or two dosages of Vitamin A, respectively. *(median (IQR))

Children who received one dose of vitamin A remained in hospital for a shorter period than those who received either no vitamin A (median 2 vs 5, p 0.01) or two doses of vitamin A (median 2 vs 3, p 0.01). (Fig 11).

Antibiotic therapy was prescribed for 169 (70.7%) children during their admission. The majority (n=103/169, 60.9%) received first line antibiotics. The duration of therapy with first line oral antibiotics was a median of 3 days (IQR 2 – 3 days), while first line intravenous was a median of 3.5 days (IQR 3 – 5). A combination of first and second line antibiotics had a median duration of 10 days (IQR 8 – 12) and first, second and third line antibiotics a median of 15.5 days (IQR 11 – 20 days).

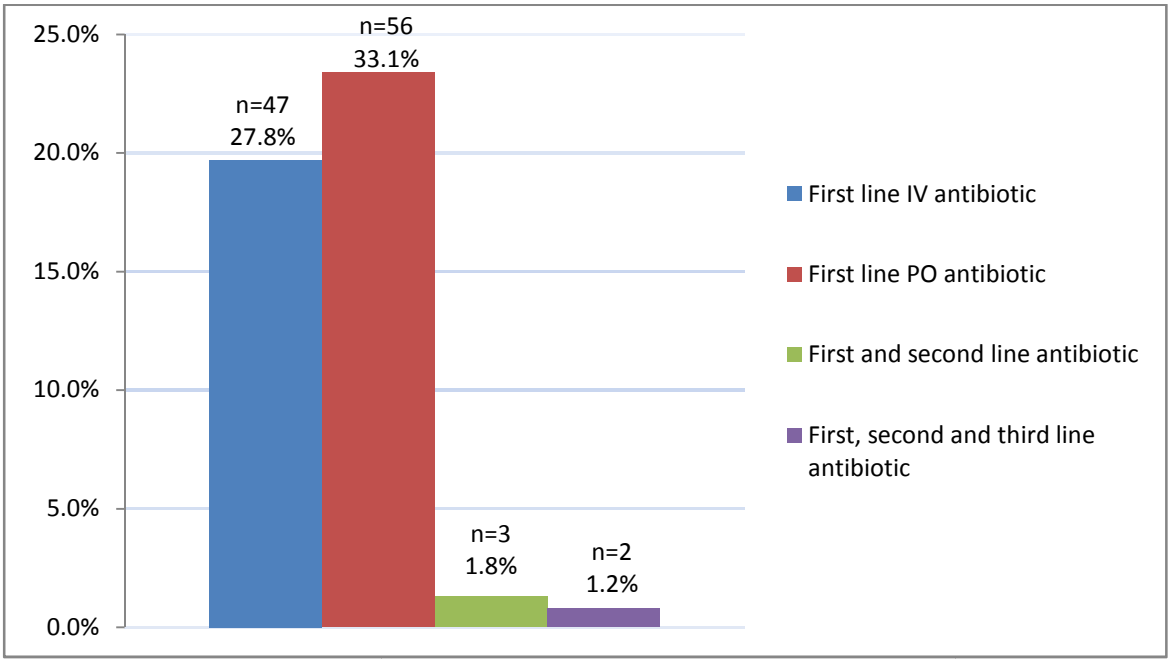

Figure 12: Number and level of anti biotics received by children during their admission for measles as percentage of those who received antibiotics (n=169).

Seven (n=7/239, 2.9%) patients required ICU care, 2 (28.6%, n=2/7) were admitted directly at presentation and 5 (71.4%) were transferred during their hospital stay. A further 3 patients required respiratory support (CPAP) (see above) outside of ICU and were not included in ICU analysis.

The median period from admission to hospital until admission to PICU was 1 day (IQR 1 – 4 days). Four (n=4/7, 57.1%) children were younger than 9 months of age at the time of PICU admission. Pneumonia (n=6/7, 85.7%) was the most common reason for admission. All 7 required invasive ventilation and 3 (n=3/7, 42.8%) also required high frequency oscillatory ventilation (HFOV). Six (n=6/7; 85.7%) patients required inotropic support. The median duration of PICU admission was 9 days (IQR 6 – 11).

Four children died with a mortality rate of 1.7% (n=4/239). The median age at death was 9 months (IQR 7 – 14 months). Pneumonia (n=3/4, 75%) was the most common cause of death. Two of the deceased children were HIV exposed uninfected and one was HIV-infected.

Results relating to HIV:

HIV exposure, as confirmed by history (from primary caretaker or as indicated on Road to Health Card) only, is shown in Figure 13.

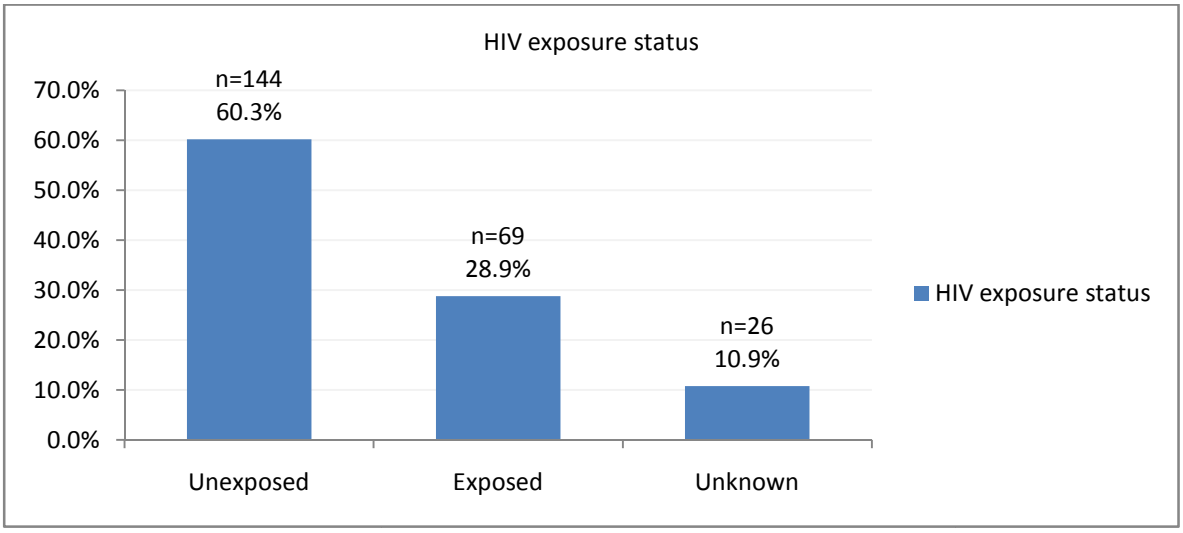

Figure 13: HIV exposure and infection status, shown as percentage of total study population. (n=239)

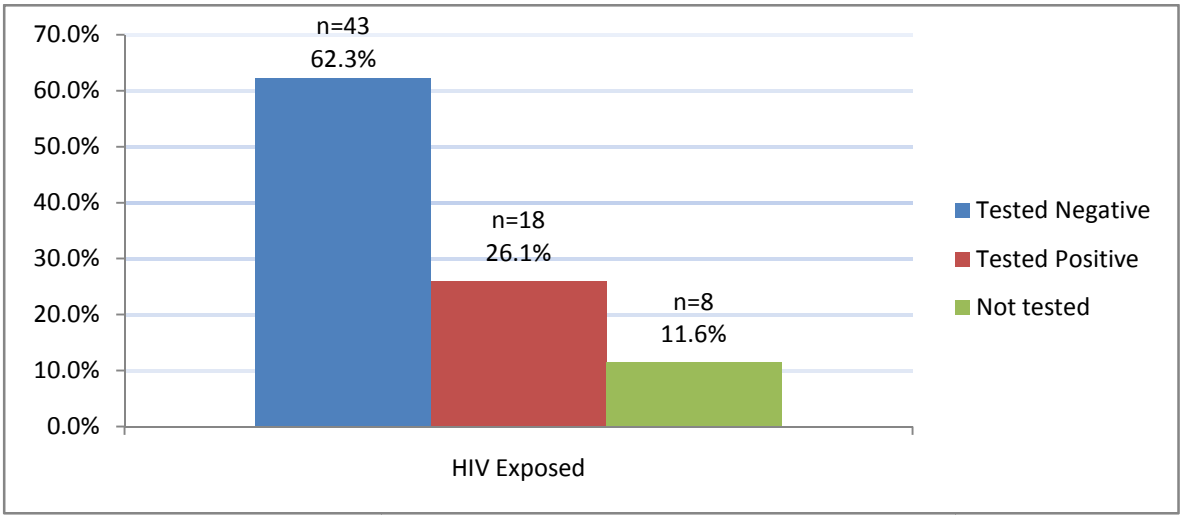

Figure 14: Confirmed HIV status of children who were known to be HIV exposed (n=69), shown as percentage of exposed group.

HIV testing was not done on 142 (59.4%, n=142/239) children. Of these children, 8 (5.6%, n=8/142) were in the HIV exposed group (n=69).

Twenty children (8.4%, n=20/239) were HIV-infected. Of these, 12 (60%, n=12/20) were on HAART at the time of admission.

Two children were recorded as HIV unexposed but found to be HIV-infected upon further testing.

HIV status according to age group is shown in Figure 15. HIV-infected children (n=20) were older than HIV-uninfected (n=72) (p=0.01) and untested (p=0.01) children. HIV-infected

children (n=20) presented at a median age of 40 (IQR 8 – 64) months, compared to 10 (IQR 6 – 15) months for HIV-uninfected children.

Six (30%, n=6/20) of the HIV-infected children had received a measles vaccination prior to presentation.

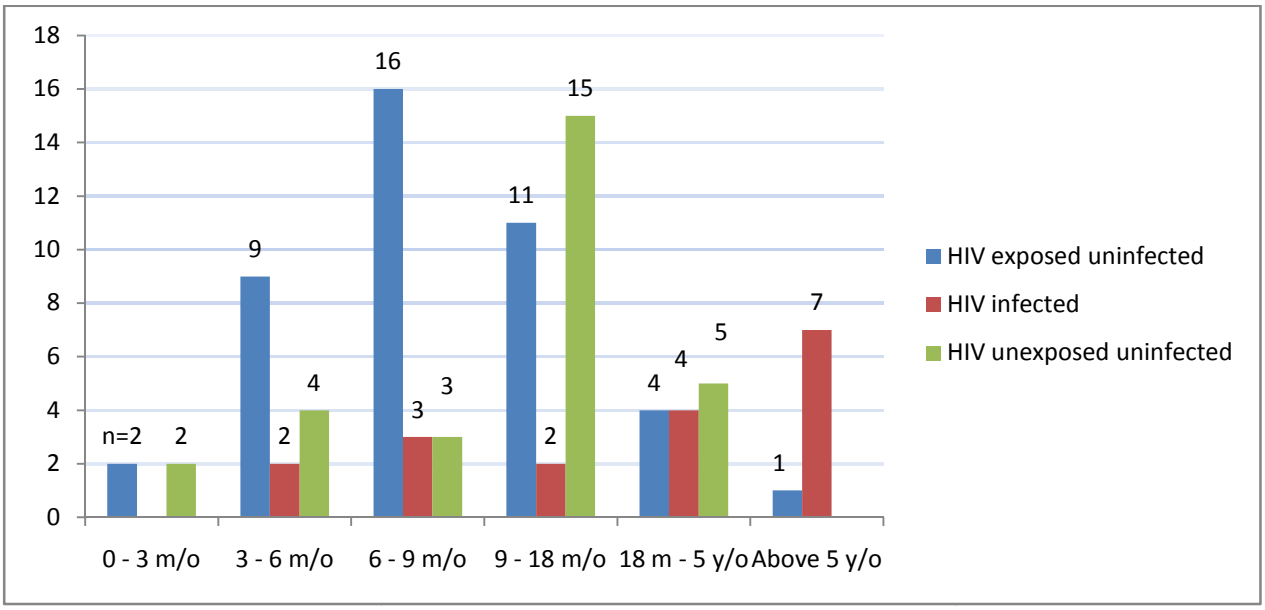

Figure 15: HIV status in HIV-exposed children per age category. (n=number of children per status in that age group) (total n=69)

Figure 16 shows nutritional status as calculated by WAZ for children <5 years old. Five (50%, n=5 /10) of HIV-infected (4 UWFA and 1 severely UWFA) and 16 (40%, n=16/ 40) of HIV-exposed uninfected children were malnourished.

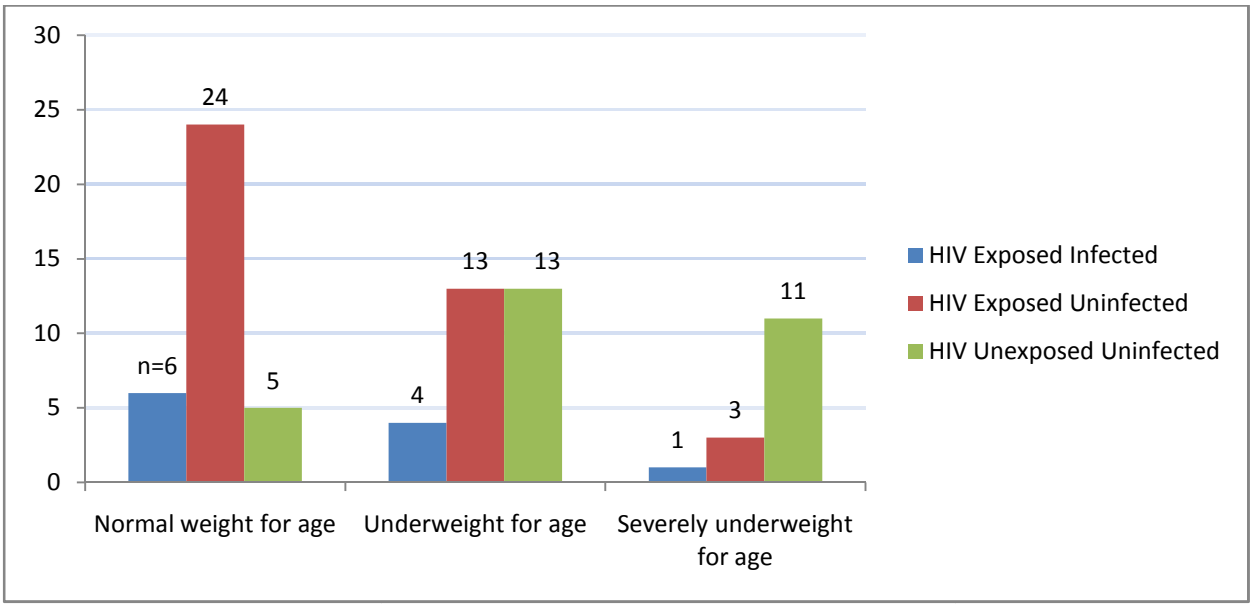

Figure 16: Weight for age compared to known HIV status as was confirmed by HIV testing (n=children per group). (One child had a weight of above Z-score +2 and is not shown in the figure.)

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	HIV Exposed Infected	HIV Exposed Uninfected	HIV Unexposed Uninfected	P value
Total number	20	43	29	
Number Admitted	18(90%)	38(88.4%)	27(93.1%)	0.802
Age at admission	40(9-64)*	8(6-14)*	10(6-15)*	0.003
Duration of hospitalisation	6(4-7)**	3(2-5)**	6(5-12)**	0.003
PICU admission	1(5%)	1(2.3%)	5(17.2%)	0.057
Death	1(5%)	1(2.3%)	2(6.9%)	0.632
One complication	5	15	12	
Two complications	10	21	14	
Three complications	2	3	2	
Four complications	1	0	0	

Table 1: Basic statistics compared with HIV infection status, p values calculated to compare all 3 groups. *Age at admission: median (IQR) months. **Duration of hospitalisation: median (IQR) days.

HIV infected children were older than HIV exposed uninfected (p <0.001), as well as HIV unexposed uninfected (p 0.02), but there was no difference between HIV exposed uninfected and HIV unexposed uninfected (p 0.85).

Those who were HIV-exposed uninfected had a shorter hospital stay than HIV-unexposed uninfected children (median 3 vs 6 days, p 0.004), however they did not have a shorter stay than HIV-infected children (p 0.14). The duration of hospitalisation was not different between HIV-infected and HIV-unexposed uninfected children (p 1.0).

Death rate was similar in the HIV-infected and -uninfected groups (0.4% (HIV-infected) vs 1.3 %(HIV-uninfected) p 0.85)).

There was no difference between number of complications and HIV exposure or infection.

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Discussion

Measles is an acute, highly contagious viral disease caused by an RNA paramyxovirus of which humans are the only natural host. Infants are protected from the infection by maternal passively acquired antibodies for the first 3 to 6 months of life. Measles is spread via respiratory droplets and incubates for 8 to 12 days after which there is a 3 to 5 day prodromal period with symptoms of upper respiratory tract infection, conjunctivitis and fever. On the fourth day the erythematous maculopapular rash appears spreading from face to trunk to limbs. The disease is communicable for 7 to 10 days from the onset of the prodrome, however, the virus can be excreted for prolonged periods in immunocompromised children. The infection causes immunosuppression through decreased cell mediated immunity. Complications include pneumonia, croup, otitis media, sinusitis, diarrhoea, encephalitis and years later subacute sclerosing panencephalitis. Measles treatment comprises vitamin A supplementation, symptomatic treatment with anti-pyretics and treatment of complications. Measles prevention rests on the provision of the measles live-attenuated virus vaccine. [2, 3]

Routine measles immunization at 9 months was introduced into the South African Expanded Program on Immunization (EPI) in 1974. In 1995 this was modified to include a second booster dose at 18 months. Despite our vaccination program this was the third measles epidemic in a 20 year period (1992, 2003, 2009). [21]

A number of measles outbreaks have been described in countries all over the world, notably first world countries like Germany, Italy and Switzerland in 2006 and 2007, the Netherlands in 2008 and Ireland in 2009-2010. [8–12] During 2009 and 2010 28 African countries experienced laboratory confirmed measles outbreaks. [22]

In our study we found low rates of measles immunisation at 31.1% and 23.8% for the 1st and 2nd immunization respectively. This would be expected in a population infected with measles. The decline in uptake from 9 months to 18 months is in agreement with other studies from the area.[23] Corrigal et al (2008) showed that reasons for not vaccinating in the Western Cape included: clinic-related factors (47%), lack of information (27%), caregiver being unable to attend the clinic (23%) and lack of motivation (14%). Of clinic factors cited, the two commonest factors were missed opportunities (34%) and being told by clinic staff to come back another time (20%). The immunization coverage was found to be 76.8% for vaccines due by 9 months and 53.2% for vaccines due by 18 months. [23] Although we did not establish the reason for low immunization uptake in our study, it is likely that the same reasons would be found. Of concern is the number of children who received immunisation that were diagnosed with the disease. With a primary vaccine failure rate of a single dose of measles vaccine estimated at <5% one needs to consider other possibilities.[4] These may include inadequate vaccine practises including poor cold chain maintenance at primary level facilities in resource limited settings.

Despite the regular availability of highly effective vaccines we still find ourselves facing measles epidemics which lead to high morbidity and mortality. Schoub postulated two reasons for the outbreaks of measles. One, the measles virus is highly contagious due to its very high basic reproductive rate and two, a very high vaccination coverage (>95% of population should receive 2 doses) is required to prevent transmission and outbreaks. [21] Bernhardt et al determined that prior to the measles vaccine campaign in 2010, 61,5% of 9

to 17 month old children had measles immunity, this number increased to 94% after the campaign. [24]

Richard et al (2007) found that 92.9% of patients in the epidemic in Switzerland (2006 – 2007) were unvaccinated. Many years of poor vaccination coverage as well as a low incidence of natural measles infection has increased the number of non-immune individuals, which contributes to the measles outbreaks. [10] In our study we had a much lower non-vaccinated rate at 49.6% (59 of 119 children qualifying for the first vaccine) for the first measles containing vaccine (9 months) and 44.4% (28 of 63 children qualifying for the second vaccine) for the second dose (18 months). At Red Cross Children's Hospital (RCCH) 45% (40/92) of children with known vaccination status, had received any measles vaccine. This raises concerns regarding vaccine practices within the Cape Town Metro area, a high number of children who developed measles had been previously immunized. Aspects of immunization administration should be investigated to elucidate the causes of this trend. Sartorius et al found an 88.1% average coverage of first measles vaccine in South Africa. An increased risk of measles infection was found in infants in populations with lower vaccine coverage rates. High population densities in metropolitan areas also increased rates of measles infection. [25]

Our study showed that this was a disease of under 5 year olds (median 9 months). Of note the highest proportion was children between six and nine months of age who did not qualify for measles vaccination according to the local EPI programme. This is in contrast to developed countries which showed an older population affected, with median age groups ranging from 9 to 11 years to 15 to 16 years. [8-12,21,22] In outbreaks during 2009 and 2010 in 5 African countries (Angola, Democratic Republic of Congo, Ethiopia, Nigeria and Sierra Leone) the majority of cases during the outbreaks involved children below 5 years of age. [20] Local data on the 2009/2010 South African measles epidemic (February 2010) showed the highest incidence of disease in the 6 to 11 month age group, with a second peak incidence in the 20 to 29 year old group. [26]

Data from 40 African countries between 2002 and 2009 showed the highest burden of disease in children 9 months to 4 years old with a median age of infection of 36 months (IQR 16 – 96 months). This is in contrast to our very young population. Forty nine percent of cases occurred in unvaccinated individuals, in agreement with our data, and raises concern about vaccination practises especially cold chain issues in Africa.

As immunisation coverage has improved the age distribution of cases has shifted to older children and young adults as seen in developed countries. However, in the infant population increased vaccine coverage has led to a decrease in age at initial infection. [27]We saw this also in our study. A number of European studies have shown that children below the age of routine vaccination form a significant percentage of children infected with measles with rates varying from 16,2% in Spain to 32% in France. [28,29,30]. These high rates of infection in children below the age of routine vaccination, is an important reminder of the effect of herd immunity on the incidence of measles epidemics. Leuridan et al showed that measles outbreaks in Europe are due to increased susceptibility in certain age groups, the presence of susceptible individuals in the community and circulating measles virus. Increase in susceptibility can be explained by primary vaccine failure, decreased vaccine coverage, waning immunity following vaccination and a lack of boosting by natural measles infection. Infants are protected by maternal antibodies for an average of three to six months. This is

usually longer in naturally immune women compared to vaccinated women. During the European measles outbreaks over the last decade a median of 10.5% of cases were in infants.[31]

Rates of malnutrition in our study were higher than published national averages. (National Food Consumption Survey (2005) South African children aged 1 to 9 years; 10.3% were UWFA and 1.4% was severely UWFA [32]). UNICEF data for South Africa shows that 9% of <5 year olds were UWFA (2007 – 2011). [33] However, Le Roux et al [34] found the WAZ was -3.3 in Cape Town townships (2006 – 2007), much lower than our mean WAZ of -0.8 which is in concordance with Le Roux et al [35] who found similar WAZ at Red Cross hospital [-0.76 (IQR -1.73 – 0.24)] during the same epidemic. Possible reasons for this are: selection bias, improved nutrition and nutrition intervention programs since the publishing of the National Food Consumption Survey (2005).

Measles is more severe in malnourished children and one would therefore suspect these children more likely to be referred with complications of the disease. Areas which refer to Tygerberg Hospital are also known to be under resourced. High case fatality ratios have been associated with malnutrition in most hospital studies on measles mortality. This association has not been documented in community studies. The most important factors associated with severe or fatal measles in these settings are overcrowding and intensive exposure. In community studies done in West Africa, Bangladesh and England several cases in a family were associated with higher measles mortality. [36] Although all sub-districts routinely draining to our hospital were represented in our study, showing a widespread epidemic, the majority of children were from Khayelitsha sub-district which referred to our hospital only for the duration of the epidemic. This area is known to be an under-resourced area within the Cape Metro with high mortality rates when compared to other sub-districts. [37]

In contrast to studies from Europe [12,28,29] and other local studies [34] which found pneumonia to be the most common complication (31% in Spain to 68% in Cape Town), we found gastroenteritis (67.3%) to be the most common although pneumonia was still significant (54,3%). Gastroenteritis rates were also high in the same Cape Town study (48%) [35], this may be a result of an overlap of the measles epidemic and the yearly gastroenteritis season in Cape Town.

Vitamin A has been shown to halve the risk of death or major complication during hospital stay, when compared to placebo [38]. Our study was in accordance with this, in that compared to children who had received no vitamin A, those who received one or two doses had a shorter length of hospitalisation. However, two doses correlated with longer hospitalisation than one dose. It is unclear why some children did not receive any vitamin A, as it was part of the provincial protocol. Many children had received Vitamin A at community clinics during early phases of their illness or prior to referral to our facility; this could explain the apparent lack of Vitamin A doses received during their care in our measles ward.

The majority of children (70.7%) received antibiotics, during their hospitalisation, presumably to treat suspected superimposed bacterial pneumonia. First line antibiotics was received by 46.4% of children, small numbers received combinations of first, second and third line antibiotics. As would be expected, longer durations of hospital stay correlated with higher antibiotic lines and increased median durations of treatment. Kabra et al in a Cochrane

review from 1966 to 2008, found that fewer children who received antibiotics prophylactically developed pneumonia than those who did not receive antibiotics (1.9% vs 6%), the number of other complications (purulent otitis media and tonsillitis) were also significantly decreased in the treatment group. Prophylactic antibiotic use is therefore suggested as beneficial in preventing complications of measles infection. [39] A study of 84 patients in West Africa showed that patients who received a prophylactic anti-biotic (Co-trimoxazole) developed less pneumonia and conjunctivitis compared to a placebo group [40]. In our ward it was protocol for any child who presented with clinical features of pneumonia to receive antibiotics, the choice of oral vs parenteral was determined by the perceived degree of clinical illness, co-morbidities present and response to treatment.

Le Roux et al [35] described the same measles epidemic as experienced at Red Cross Children's Hospital (RCCH) in the Cape Town Metro West District. We showed an admission rate 1.5 times higher than their study (79% vs 30%). Factors which may have influenced admission rates include: TBH had a dedicated referral ward for complicated measles cases (in Metro West this was opened at New Somerset Hospital not RCCH). Khayelitsha sub-district (known to have a high burden of disease and high mortality rate [37]) referred directly to our ward for the duration of the epidemic. RCCH patients were younger at admission (median age 7.3 months vs 9 months in our study) with more children < 9 months of age (65% vs 50.2%). We only described the first 2 months of the epidemic, had we been able to include all 1700 admissions over the entire epidemic our results may have differed.

Our study showed a HIV infection rate of 20.6% (n=20 of 97 children who did have HIV testing) in contrast to Le Roux et al who showed 14% [35], of concern is that 59.4% of children in our study never had a test for HIV despite the high incidence in our community. Children who were not tested for HIV had a shorter hospital stay as well as fewer complications and therefore may have been perceived as having less significant disease. It is important for us to re-emphasize the need for provider initiated counselling and testing for HIV infection at any and all healthcare visits.

Our mortality rate was almost half that of the Red Cross study (1.7% vs 3%). In the RCCH study population 18% of HIV-infected children and 3% of HIV-uninfected children died versus 5% and 4.2% respectively in our study population. The HIV-infected child who died at Tygerberg was not on HAART at the time of admission. There was a total of 18 deaths at TBH for the period the ward was open, 2 of which were HIV-infected (11.1%). It is unclear what caused the lower mortality rate in our study, possible causes may include referral pathways and differences between subdistricts.

In the last 20 years the proportion of vaccinated individuals has increased and is replacing those with immunity related to natural infection. [41] As a result maternally acquired antibodies are decreasing and are catabolised earlier due to the poorer quality of vaccine-induced immunity. This causes an increased risk of infection in infants at a younger age, [42] as shown in our study with 50.2% of our study population younger than 9 months.

The risk of measles prior to the age of routine vaccination is increased in infants born to HIV-infected mothers due to decreased presence of passively acquired antibodies [6]. The average age of admission in our study was 8 months in HIV exposed, uninfected infants and 10 months in HIV unexposed, uninfected infants. Therefore showing the trend of HIV exposed children to develop the measles infection earlier than their unexposed counterparts.

Further research is required to determine possible causes for the older age of HIV-infected children (40 months) who acquired measles infection. However we can postulate that this may be as a result of delayed initiation of HAART prior to implementation of current guidelines with possible vaccine failure in immunocompromised children. Other possible factors could include the decreasing number of HIV infected infants due to improved Prevention-of-Mother-to-Child practises. A study from Central Africa [43] showed that antibody titres were lower in HIV-infected children, particularly if combined with a low CD4+ T lymphocyte count. Factors influencing measles vaccine effectiveness include the age at introduction of HAART and the time since last vaccination.[43] At the University of Warsaw children with immune recovery after initiation of HAART developed protective antibodies after revaccination.[44] This was the first large nationwide measles epidemic since the onset of the HIV epidemic in South Africa. It is currently not standard practice in South Africa to revaccinate HIV-infected children, however the role of timing of ARV initiation, immunisation schedule with possible earlier immunization and boosters in immune-compromised children should be investigated.

Whilst the risk of acquiring measles infection is greater in HIV-infected children [5], our study did not show a clear increased rate of measles infection in the HIV-infected cohort of our study population. The rates of complications were the same for all children regardless of HIV exposure and infection status. We also showed that mortality was not increased in HIV-infected children.

Research from a Thai orphanage during a measles outbreak comparing HIV-infected and HIV-uninfected showed that children proven to have protective measles antibodies after re-immunization (ie post ARV therapy initiation) did not contract measles, thus the main factor correlating with risk of acquiring measles infection was immunization status and not HIV infection status. [5]

Our study has several limitations. A small patient population was examined. The study was retrospective, with difficulty in obtaining some patient folders. The diagnosis of measles was based on clinical case definition and not laboratory confirmed, however at the time of the epidemic this was Western Cape policy. Our study took place in the Paediatric Department and thus was limited to children under 13 years of age, this leads to bias in the interpretation of certain results relating to the age distribution of the population vulnerable to measles infection. Despite these limitations our study gives a good overview of the epidemic and our results compare favourably with other studies in similar settings.

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Conclusion

We have described a young group of children affected by measles in this epidemic. There were significant morbidity and mortality with respiratory illnesses accounting for a large number of complications and deaths. Gastroenteritis was the most common complication which differs from other studies.

HIV infection did not increase morbidity and mortality due to measles co-infection. However older age of HIV-infected children may suggest re-immunization of HIV-infected individuals is required. Ours was a small patient population and we had a high number of children with unknown HIV status, therefore further research is needed to determine whether this relationship is truly accurate.

A significant number of children were not tested for HIV during hospitalization despite the high prevalence of disease in our community. In future we should be more vigilant regarding screening every child for HIV disease at each contact with medical care in order to also improve the outcome of HIV disease.

Due to this measles epidemic South Africa now has a large cohort of young citizens that have gained natural immunity to measles, however if our vaccination rates and practises do not improve we are likely to experience more measles epidemics in future.

Interventions to improve vaccination rates and practises are required and further research is needed to determine whether the first measles vaccine dose should be given at 6 months rather than 9 months of age. Opportunities at every level of the healthcare system should be utilized to increase the rate and effectiveness of vaccination. All health care workers should be vigilant in checking the vaccination status of all children at all follow-ups. Vaccinators should also have adequate training in vaccine practises especially regarding cold chain management.

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