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A RETROSPECTIVE REVIEW OF PATIENTS ADMITTED TO THE
PAEDIATRIC ICU AT RED CROSS WAR MEMORIAL CHILDREN’S
HOSPITAL DURING 2010 WITH THE CLINICAL DIAGNOSIS OF
MEASLES OR MEASLES-RELATED COMPLICATIONS

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DECLARATION

I, [Signature], hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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PART A: PROTOCOL

LITERATURE REVIEW

A) DISEASE OVERVIEW

The measles virus, also known as rubeola, is an RNA virus in the family Paramyxoviridae, genus Morbilivirus. It is spread via aerosolized respiratory droplets or direct contact with respiratory secretions. Risk factors for infection include unvaccinated children, infants who lose passive immunity prior to the age of routine immunization, children with immunodeficiency and travel to endemic areas. Initial infection and viral replication occur locally in tracheal and bronchial epithelial cells. After 2-4 days, the virus infects local lymphatic tissues and after amplification in the regional lymph nodes disseminate to various organs. Measles infection causes immunosuppression that persists for weeks to months after the acute infection. This may predispose individuals to severe bacterial infection, especially bronchopneumonia, which is a major cause of measles-related mortality among younger children [1, 2]. Case-fatality rates are highest in young children under 5 years of age and in immunocompromised children. Other risk factors for severe measles and its complications in children include malnutrition and vitamin A deficiency.

The diagnosis of measles infection is made by serology or virus isolation from respiratory secretions, blood or urine. A chest X-ray (CXR) should be performed if pneumonia is suspected and a lumbar puncture if encephalitis is suspected [3].

The treatment of measles is largely supportive, including oxygen therapy, maintenance of hydration, and antipyretics for fever control and patient comfort. Vitamin A administration has been associated with reduction in morbidity and mortality. Routine prophylactic antimicrobial treatment is not indicated. Acyclovir is recommended for herpes stomatitis and post-measles croup due to herpes virus infection [4].

Prevention of measles can be achieved by the administration of the measles vaccine or human immunoglobulin. In addition, susceptible individuals should avoid measles patients during their infectious period. In hospitals, measles cases should be isolated and standard and airborne precautions should be observed during their admission.

Measles vaccination as part of the Expanded Programme on Immunisation (EPI) in South Africa is routinely administered at 9 months and 18 months of age. The monovalent preparation is used in the public sector, while the combined measles-mumps-rubella (MMR) vaccine is readily available in the private sector. The vaccine is also effective in prevention or modification of measles if given within 72 hours of exposure. Immunoglobulin (IVIG) may be given up to 6 days following exposure to prevent or modify infection. Immunocompetent children should receive
0.25ml/kg IM and immunocompromised children 0.5ml/kg IM. IVIG is indicated for susceptible household contacts of measles patients, especially infants < 6 months of age, pregnant women and immunocompromised individuals [1, 2, 5].

**B) GENERAL CONSIDERATIONS**

Measles is a highly communicable disease. It is one of the leading causes of death among young children even though a safe and cost-effective vaccine is available [6]. In 2008 there were still 164 000 measles deaths globally; with an estimated 85% of these deaths occurring in Africa and South East Asia [7].

The measles epidemic that occurred in 2009-2010 highlights the importance of establishing case-based, laboratory-confirmed surveillance as we attempt to move from control to elimination. Discussions about measles eradication has continued, most recently at a World Health Organization (WHO) meeting on measles in which conclusions encouraged a revised target of 2020 for measles eradication [9].

South Africa is a developing country that faces several challenges in providing adequate health care and achieving the Millennium Development Goals (MDG). In addition to the HIV and tuberculosis epidemics, a very high burden of morbidity and mortality results from poverty-associated violence and injury, chronic diseases, food insecurity and malnutrition, poor access to health care and high maternal, neonatal and child mortality [10].

The 2009-2010 measles epidemic had a profound impact on childhood morbidity and mortality in South Africa. According to the National Institute for Communicable Diseases (NICD) a total of 18 396 proven measles cases countrywide were reported from January 2009 to 8 February 2011. 2009 of these cases occurred in the Western Cape (11%). Children under 1 year of age had the highest incidence of infection [11]. In 2002, a hospital-based study in the Gauteng and Western Cape provinces noted a 96% decrease in admitted cases after a catch-up measles vaccination campaign in 1996-1997 [12]. However, despite 2 rounds of the national supplementary measles vaccination campaign for children aged 6 months to 15 years in April and May 2010, reports suggest that there was poor acceptance on the part of some parents and certain schools [13]. Vaccine coverage depends strongly on the acceptance of vaccination by parents and access to the health care system. Parents may consider the potential benefits for the community (i.e. herd immunity effects and a reduced economical burden) as less important than the individual risk from potential vaccination side-effects [14]. Clearly there is a need for ongoing promotional campaigns not only in the public sector, but also in the private sector, bearing in mind that a major deterrent to immunization in developing nations lies with the lack of monetary resources to purchase vaccines and with the lack of the organization and infrastructure to carry it out. Similarly a strategy to encourage cross-country cooperation is warranted given the high levels of immigration to South Africa.
C) MEASLES IN SOUTH AFRICAN PICU

Intensive Care Unit (ICU) facilities are expensive and consequently availability is very often limited in developing countries. Determination of disease specific outcomes, e.g. length of ICU stay and mortality may be useful to allow cost-effective allocation of these limited resources. However, in developing countries, like South Africa, little data has been generated about the outcome for children admitted to Paediatric ICU’s (PICU’s). Also, little recent data is available from South Africa about the impact of measles and its complications on ICU resources. Measles accounted for 19.7% of the total number of PICU admissions over a 25-year period (1971-1995) in a Durban- based study, with mortality rates of up to 66%. This experience was similar to those described from Zambia and Zimbabwe, also developing countries [15].

Reynolds and Klein published a study in 1987 about how the hospital functions as a vector of measles in the community. Over a 16-month period the authors surveyed a total of 77 consecutive cases of life-threatening measles admitted to the PICU at Red Cross War Memorial Children’s Hospital. 28 of these children died and 9 developed chronic lung disease. 20 of the 77 patients contracted the disease in the hospital. Of these, 50% died compared with 32% of the patients who acquired measles in the community. The authors concluded that hospitals can contribute substantially to the spread of measles in the community [16].

D) MEASLES AND HIV INFECTION

A South African study conducted in the paediatric isolation units at King Edward and Clairwood Hospitals in Durban between 1985 and 1996 found that measles accounted for the majority of admissions (58%). Between 1994 and 1996, 1% of measles cases were associated with HIV-1 infection and this resulted in 56% of measles deaths in those patients [19]. HIV is a major health burden in South Africa [20, 21], with HIV prevalence among infants 0-2 years of 2.1%, and 3.3% average in the age group 0-4 years. The lowest prevalence was found in the Western Cape (< 1%) [22].

It has been postulated that, in regions with high HIV prevalence, measles transmission may be sustained despite high immunization coverage rates, since HIV infected children have an early decline in maternal antibody titers resulting in susceptibility to measles at a younger age [23]. They also have higher rates of measles vaccine failure and measles antibodies decline more rapidly after immunization compared with HIV uninfected children [24]. This could lead to a greater proportion of susceptible children and these findings support the WHO recommendation to provide the first dose of measles vaccine to HIV infected children at 6 months of age. Data from Kenya and Zambia illustrates that HIV infection may alter how measles virus is transmitted within a population. HIV infected children may not develop the characteristic measles rash and
this could result in unrecognized transmission of the measles virus. They may also have prolonged shedding of the measles virus and hence increased duration of infectiousness [25].

**OBJECTIVES**

The aims of this study are to describe the incidence, patient profile, course and outcome of patients admitted to the PICU of Red Cross War Memorial Children’s Hospital with measles or measles related diseases, and to determine the impact of the 2010 measles epidemic on PICU resources.

**METHODS**

Inclusion criteria: all patients admitted to the PICU from January to December 2010 with the clinical diagnosis of measles.

Exclusion criteria: none.

Study design: retrospective descriptive study.

Clinical folders of eligible patients identified from the PICU database will be reviewed and data recorded on a standardized data collection form (Addendum A).

Associated costs will be calculated using bed days utilized and estimated daily PICU admission cost.

Recorded data will be transcribed to an Excel database. Descriptive data, including testing of normality of distribution, will be conducted. Comparisons of the primary and secondary outcome measures will be made by means of the Mann Whitney U test for non-parametric data, or the Student’s T-test for normally distributed data. Pearson’s Product Moment or Spearman’s rank order correlation tests will be used to assess relationships between variables. The hypothesis of independence between variables will be tested using Chi-Square tests. The findings will be reported in an article that will be presented at an internal Red Cross Children’s Hospital PICU journal club and it will subsequently be submitted for publication. It will also be submitted as an M Phil thesis.
ETHICS

Ethical approval will be obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, before initiating this study. Considering that this study is a retrospective audit of care which will in no way affect patient management or outcome, consent will not be obtained from participants or their caregivers. Confidentiality will be ensured and no patient identification will occur in any output arising from this research. All research will adhere to the requirements stated in the Declaration of Helsinki (2008) [26].

Of note is to mention that the existing South African ethical-legal framework for research with children is in a state of flux as key legislation governing research with children must still be enacted. Furthermore, there are inconsistencies between the proposed legislation and existing ethical guidelines. It is therefore important that researchers and the Human Research Ethics Committee attend to these discrepancies to the best of their ability and not allow the current uncertainty to discourage necessary research among children [27].
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PART B: LITERATURE REVIEW

1. CONCISE OVERVIEW OF MEASLES

Measles virus is a RNA virus in the family Paramyxoviridae, genus Morbillivirus. It is also known as rubeola (1). It is spread via aerosolized respiratory droplets or direct contact with respiratory secretions. Approximately 90% of exposed susceptible individuals develop measles (2). Risk factors for infection include unvaccinated children, infants who lose passive immunity prior to the age of routine immunization, children with immunodeficiency (due to HIV, malignancy, corticosteroid use, etc.) and travel to areas where measles is endemic (1, 3). Initial infection and viral replication occur locally in tracheal and bronchial epithelial cells. After two to four days, the virus infects local lymphatic tissues and after amplification in the regional lymph nodes disseminates to various organs (2). Measles infection causes immunosuppression that persists for weeks to months after the acute infection. This may predispose individuals to severe bacterial infection, especially bronchopneumonia, which is a major cause of measles-related mortality among younger children (1).

After an incubation period of eight to twelve days, the prodromal phase begins with fever, malaise, anorexia and coryza, conjunctivitis with photophobia and cough (the “3 C’s”) (2, 4). This is followed by an enanthem, i.e. Koplik spots (discrete red lesions with bluish-white spots in the center; on the buccal mucosa at the level of the premolars). It is the pathognomonic sign of measles and appears one to four days prior to the onset of the skin rash. The exanthematous phase occurs next, visible as an erythematous maculopapular rash that begins around the hairline and behind the ears and then spreads to the torso and extremities. The rash frequently becomes confluent on the face and upper trunk. It fades over about seven days in the same progression as it evolved, often with fine desquamation of the skin. Generalized lymphadenopathy and mild hepatomegaly may also be present. Patients are infectious from five days before the rash to four days after its onset. People who recover from measles are immune for the rest of their lives (1, 3).

Typical measles is unlikely to be confused with other illnesses, but measles in the later stages or subclinical cases may be confused with a number of other exanthematous infections and immune-mediated illnesses, e.g. rubella, adenovirus, enterovirus, EBV, erythema infectiosum, Mycoplasma, group A Streptococcal infection, Kawasaki syndrome, etc. (1, 2, 4). Common complications of measles include acute otitis media, pneumonia, laryngotraechobronchitis, transient loss of skin test responsiveness to purified tuberculin antigen, blindness, diarrhoea and encephalitis (1, 2, 4). Rare complications include haemorrhagic or “black measles”, purpura fulminans, myocarditis, hepatitis and subacute sclerosing panencephalitis (SSPE) (1, 2, 4). Case-fatality rates are higher among children younger than five years of age, with the highest mortality...
among infants aged four to twelve months and in immunocompromised children (1, 3). Other risk factors for increased morbidity and mortality include malnutrition, vitamin A deficiency and pregnancy.

The diagnosis of measles infection is made by the clinical picture described above (1, 2, 4). Laboratory confirmation is necessary for public health surveillance and outbreak control (1). The diagnosis is confirmed by serology or virus isolation. Measles IgM antibody assay is the quickest method to confirm acute measles. Measles can also be confirmed by demonstrating more than a four-fold rise in IgG antibodies between acute and convalescent sera. The virus can be isolated from respiratory secretions, blood or urine (1, 2, 4). A Measles PCR is also available and is most useful in the first few days of illness when serology may be negative. It’s also useful in severely immunocompromised patients where antibody response is often unreliable (5). A chest X-ray (CXR) should be performed if pneumonia is suspected and a lumbar puncture if encephalitis is suspected (1, 2).

The treatment of measles is largely supportive with maintenance of oxygenation and hydration, as well as antipyretics for fever control and patient comfort (1, 2, 4). Vitamin A administration has been associated with reduction in morbidity and mortality (3). Two doses of Vitamin A given 24 hours apart are recommended. Indications include children six months to two years of age hospitalized with measles and its complications, as well as children over six months of age with any of the following risk factors: immunodeficiency, clinical evidence of vitamin A deficiency, impaired intestinal absorption, malnutrition and immigration from areas with high mortality rates due to measles. Prophylactic antimicrobial treatment to prevent bacterial infection is not indicated, but antibiotics should be considered if examination and investigations suggest acute otitis media or bacterial pneumonia (1, 4). Acyclovir is recommended for herpes stomatitis and post-measles croup due to herpes virus infection.

Prevention of measles can be achieved by the administration of the measles vaccine or human immunoglobulin (1, 2). In addition, susceptible individuals should avoid measles patients during their infectious period. In hospitals, measles cases should be isolated and standard and airborne precautions should be observed during their infectious period (1, 2). Monovalent measles vaccine can be given to infants between six to twelve months of age (6). However, such infants require an additional two doses of measles vaccine after their first birthdays because of the reduced efficacy of the vaccine when administered before 12 months of age (due to potential interference by maternal antibodies). The American Academy of Pediatrics therefore recommends that children immunized prior to one year of age should receive two additional doses at 12-15 months of age and four to six years of age (6). A single dose of measles vaccine administered to a child older than 12 months induces protective immunity in 95% of recipients (1). Measles vaccine as part of the Expanded Programme on Immunisation (EPI) in South Africa is routinely administered at nine months and 18 months of age (7). The monovalent preparation is used in the public sector, while the combined measles-mumps-rubella (MMR) vaccine is readily available in the private sector. The vaccine is also effective in prevention or modification of measles if given
within 72 hours of exposure (1, 2, 4). Intramuscular (IM) immunoglobulin (IVIG) may be given up to six days following exposure to prevent or modify infection. Immunocompetent children should receive 0.25ml/kg IM and immunocompromised children 0.5ml/kg IM. IVIG is indicated for susceptible household contacts of measles patients, especially infants less than six months of age, pregnant women and immunocompromised persons (1, 2, 4).

2. CONTEXTUALIZATION OF MEASLES IN SOUTH AFRICA

Measles is a highly communicable disease. It is one of the leading causes of death among young children even though a safe and cost-effective vaccine is available (3). Because measles is highly contagious, a five percent susceptible population is sufficient to sustain periodic outbreaks in otherwise highly vaccinated populations. The implementation of measles vaccination programs since 1966 greatly reduced the number of reported cases (8). Measles vaccination resulted in a 78% decrease in measles deaths worldwide between 2000 and 2008. However, in 2008 there were still 164 000 measles deaths globally; an estimated 85% of these deaths occurred in Africa and South East Asia (9). In 2009-2010 South Africa was struck by another measles epidemic (last epidemic occurred in 1992). This potentially has the implication that the World Health Organization (WHO) fourth Millennium Development Goal (MDG 4) which aims to reduce the under-five mortality rate by $\frac{2}{3}$ between 1990 and 2015 may not be met, as routine measles vaccination coverage has been selected as one of the indicators of progress towards achieving MDG 4 (10).

The WHO and UNICEF collaborated to reduce global measles deaths by 90% by the year 2010. The goals of their program included the following:

- Routine immunizations for children by one year of age
- Second opportunity for measles immunization through mass vaccination campaigns to ensure that all children receive at least one dose of the vaccine
- Effective surveillance in all countries to recognize and early response to measles outbreaks
- Enhanced treatment of measles, including vitamin A (1, 3)

Despite the comprehensive WHO and UNICEF measles mortality reduction strategy and the Measles Initiative, certain high-burden countries in sub-Saharan Africa continue to face recurrent epidemics and unacceptably high mortality from a completely preventable disease, e.g. during the 2004-2005 measles epidemic in Niger, Nigeria and Chad (11), and the 2009-2010 measles epidemic in South Africa. Discussions about measles eradication has continued, most recently at a WHO meeting on measles in which conclusions encouraged a revised target of 2020 for measles eradication (12).
South Africa is a developing country that faces several challenges in providing adequate health care and achieving the MDG’s (10). In addition to the HIV and tuberculosis epidemics, a very high burden of morbidity and mortality results from violence and injury, chronic diseases and maternal, neonatal and child mortality (10). The Child Healthcare Problem Identification Programme (CHIP) data shows that 51% of child deaths had laboratory confirmed or stage III/IV signs of HIV infection and that HIV-infected children have a significantly higher morbidity and mortality. (10). Food security and dietary quality still remain a challenge for many South Africans. According to CHIP data, \( \frac{1}{3} \) of children who died were severely malnourished and over 60% were underweight for age. Poverty is linked to all these challenges. Mothers, babies and children in poor families are at increased risk of illness and face more challenges in accessing quality health care timely, with the result that poor children are at least four times more likely to die than children from more affluent families. Child mortality is twice as high in the rural Eastern Cape compared with the more urban Western Cape, and four times higher for black children than for white children (10). A comparison of measles complications in well-nourished and malnourished children in Pakistan demonstrated that complications of measles occur far more frequently in undernourished children (13).

The 2009-2010 measles epidemic had a profound impact on childhood morbidity and mortality in South Africa. According to the National Institute for Communicable Diseases (NICD) a total of 18 396 proven measles cases countrywide were reported from January 2009 to February 2011 (14). Two thousand and nine of these cases occurred in the Western Cape (11%). The first case in the Western Cape was confirmed in September 2009. Children under one year of age had the highest incidence of infection, as well as the highest mortality. At Red Cross War Memorial Children’s Hospital (RXH) alone there were a total of 552 hospital admissions from November 2009 to 31 July 2010; the most common indications for admission were pneumonia (63%) and severe diarrhoea (47%) (15).

In 2002, a hospital-based study in the Gauteng and Western Cape provinces noted a 96% decrease in admitted cases after a catch-up measles vaccination campaign in 1996-1997 (16). A survey conducted in the Western Cape in 2005 estimated that 93% of children had received the first dose of measles vaccine, but only 60% had a second dose (17). The authors came to the conclusion that routine coverage in the Western Cape was too low to prevent a measles outbreak. Despite two rounds of the national supplementary measles vaccination campaign for children aged six months to 15 years in April and May 2010, reports suggest that there was poor acceptance on the part of some parents and certain schools (18). Vaccine coverage depends strongly on the acceptance of vaccination by parents and access to the health care system. Parents may consider the potential benefits for the community (i.e. herd immunity effects and a reduced economic burden) as less important than the individual risk from potential vaccination side-effects (19). This is a problem that is potentially even more pronounced in developed countries, as documented by a study conducted in San Diego, US in 2008 which showed that measles outbreaks can occur among clusters of intentionally under-vaccinated children at major
cost to medical systems and public health agencies (20). Clearly there is a need for ongoing promotional campaigns not only in the public sector, but also in the private sector, bearing in mind that a major deterrent to immunization in developing nations lies with the lack of monetary resources to purchase vaccines and with the lack of the organization and infrastructure to carry it out. Similarly a strategy to encourage cross-country cooperation is warranted given the high levels of immigration to South Africa.

3. METHODS AND SEARCH STRATEGY

Owing to the paucity of current data on this topic, this was a structured literature review including all relevant literature, with no specific exclusion criteria other than language. Journal articles, electronic articles, clinical trials and policy documents in the English language were searched for using PUBMED, MEDLINE and Google search engines. The following search terms were used: “measles” OR “measles-related complications” OR “measles-related disease” OR “measles AND pneumonia” OR “measles AND laryngotracheobronchitis” OR “measles AND ICU” OR “measles AND mechanical ventilation” OR “measles AND HIV” OR ”measles AND prevention” with the modifying terms “pediatric”, “paediatric”, “child” and “infant”. Reference lists of identified articles were scanned for other relevant literature. Paediatric and paediatric intensive care textbooks were also consulted.

Where applicable, it was planned that the level of evidence for statements would be given and the literature critically appraised for scientific quality or rigor.

4. SEARCH RESULTS & QUALITY CRITERIA

One hundred and ninety-four references were identified on the initial searches, and the abstracts of these were screened. Twenty- one studies were included as relevant to this review (see Appendix A). All included studies were retrospective audits (very low evidence level using the GRADE criteria), and therefore further critical appraisal was not possible. Included studies are discussed below in narrative form.
5. SYNTHESIS

MEASLES IN PAEDIATRIC INTENSIVE CARE UNITS

Intensive care unit (ICU) facilities are expensive and consequently availability is very often limited in developing countries. Determination of disease specific outcomes, e.g. length of ICU stay and mortality may be useful to allow cost-effective allocation of these limited resources. However, in developing countries, like South Africa, little data have been generated about the outcome for children admitted to Paediatric ICU’s (PICU’s). Also, little recent data are available from South Africa about the impact of measles and its complications on ICU resources. In a retrospective descriptive study conducted in 1997 at King Edward Hospital in Durban, the investigators reviewed the admission patterns and outcomes in their PICU over a 25-year period (1971-1995) (21). They found that measles accounted for 19.7% of the total number of admissions. The patients with measles infection presented either with laryngotracheobronchitis (LTB) or pneumonia; with mortality rates of 19% and 66%, respectively.

Reynolds and Klein published a retrospective descriptive study in 1987 about the hospital as a vector of measles in the community (22). Over a 16-month period the authors surveyed a total of 77 consecutive cases of life-threatening measles admitted to the PICU at RXH. Twenty-eight (36.4%) of these children died and nine (11.7%) developed chronic lung disease. Twenty of the 77 patients (26.0%) contracted the disease in the hospital. Of these, 50% died compared with 32% of the patients who acquired measles in the community. The authors concluded that hospitals can contribute substantially to the spread of measles in the community.

An earlier retrospective descriptive study conducted at King Edward Hospital in Durban in 1976, focused on children with measles-associated pneumonia which was severe enough to require ventilation over a two-year period (1972-1974) (23). They found that these patients had a mortality rate of 64% and that complications like anaemia, diarrhoea and cardiac failure occurred in 78% of the patients, which contributed to poor prognosis. Primary measles pneumonia was identified in 30% of patients and adenovirus pneumonia in 40% of patients. Confounding factors in this study would include the small number of patients enrolled in the study (50 in total) and the fact that all of these patients had tracheostomies. Ventilation strategies were not described in detail and it seems that relatively high arterial partial pressures of oxygen (PaO2) were aimed for (70-120mmHg), thus oxygen toxicity may have contributed to morbidity. In addition, a relatively liberal transfusion strategy was used (transfusion threshold of Hb less than 9 g/dl) (24) and we know from recent studies that blood transfusions cause immunomodulation and have been identified as an independent risk factor for morbidity, mortality and nosocomial infections (25).

Another retrospective descriptive study conducted in the early 90’s at the Children’s Hospital in Los Angeles, US, evaluated the demographic and clinical correlates of laryngotracheobronchitis (LTB) as a complication of measles during a community-wide epidemic over a six-month period in 1990 (26). Of the total 440 patients with measles, 18.6% had LTB. Seventeen-point-three
percent of the LTB patients admitted to hospital required intensive care and 11% required endotracheal intubation and mechanical ventilation.

An outbreak of measles occurred in Ireland between December 1999 and July 2000 (27). A retrospective chart review for this period was conducted at the Children’s University Hospital in Dublin. The investigators identified 355 admissions with a serological or clinical diagnosis of measles. The major indications for hospital admission were dehydration (79%) and pneumonia or pneumonitis (47%). Of those admitted, 11.7% required PICU admission and seven patients required mechanical ventilation. Three deaths occurred as a result of measles.

The PICU of Soroka Medical Center in Beer-Sheva, Israel published a case series in 1995 on 15 of 237 hospitalized children with measles that required PICU care (28). All 15 patients required mechanical ventilation for pneumonia causing severe respiratory distress. The most severe complications were acute respiratory distress syndrome (ARDS) and air leaks. Four patients died; all of these had ARDS.

A similar chart review from June 1989 to June 1990 conducted at the Loma Linda University Medical Center in California showed that the most common reason for PICU admission and mechanical ventilation was pneumonia and refractory hypoxemia (47% of patients included) (29). These patients had a mortality of 56%, while the patients with LTB alone all survived.

It appears from the above data that children admitted to PICU with measles-related complications have a high mortality rate, especially when requiring ventilation for pneumonia and when measles was acquired nosocomially. The patients with LTB seemed to have better outcomes.

**MEASLES AND HIV INFECTION**

A South African retrospective descriptive study conducted in the paediatric isolation units at King Edward and Clairwood Hospitals in Durban between 1985 and 1996 found that measles accounted for the majority of admissions (58%) (30). Between 1994 and 1996, one percent of measles cases were associated with HIV-1 infection and this resulted in 56% of measles deaths occurring in HIV co-infected children. HIV is a major health burden in South Africa, especially since the country continues to be home to the world’s largest population of people living with HIV: an estimated 5.7 million people in 2007 (31). A Department of Health study conducted in 2009 estimated that 29.4% of pregnant women aged 15-49 years were living with HIV infection (32). Findings from a national HIV prevalence population survey were released in 2010 (33). This survey found that the HIV prevalence among infants zero to two years was two-point-one percent, which is lower than the three-point-three percent average in the age group zero to four years. The lowest prevalence was found in the Western Cape (less than one percent).
A study conducted in Zambia investigated the possible impact of the HIV-1 epidemic on measles in a developing country (34). The authors postulated that, in regions with high HIV prevalence, measles transmission may be sustained despite high immunization coverage rates since HIV infected children have an early decline in maternal antibody titers resulting in susceptibility to measles at a younger age. Maternally derived protection against measles may also be impaired relating to the quality rather than the quantity of the transplacental antibodies (35). HIV infected children have deficient cellular and humoral immunity, as well as impaired innate immune responses. They also have higher rates of measles vaccine failure and measles antibodies decline more rapidly after immunization compared with HIV uninfected children (36). This could lead to a greater proportion of susceptible children and these findings support the WHO recommendation to provide the first dose of measles vaccine to HIV infected children at six months of age. A multicenter randomized open label trial in the US evaluated the immunogenicity of two measles vaccination regimens: monovalent measles vaccine (Attenuvax) at six months of age and measles-mumps-rubella (MMR) at 12 months of age, or only MMR at 12 months of age in both HIV infected and uninfected children in the pre-HAART period. They found that Attenuvax at six months of age was well tolerated and sufficiently immunogenic in HIV infected children (37). Data from Kenya and Zambia illustrates that HIV infection may alter how measles virus is transmitted within a population. HIV infected children may not develop the characteristic measles rash and this could result in unrecognized transmission of the measles virus. They may also have prolonged shedding of the measles virus and hence increased duration of infectiousness (38).

6. NEEDS FOR FURTHER RESEARCH

- Efficacy and safety of earlier vaccination (first dose at six months of age) in prevention of measles in the community, as well as practical implementation and monitoring of this strategy
- Efficacy, timing and safety of earlier vaccination in HIV-infected paediatric populations specifically
- Prevention of hospital-acquired measles (for both patients and staff), as well as practical implementation, monitoring and cost implications of this strategy
- Impact of MRD and other vaccine-preventable diseases on PICU resources in South Africa and other developing countries
- Comparison of outcomes from MRD in HIV-infected vs. HIV-uninfected patients
7. **SUMMARY**

Measles is a highly communicable disease and one of the leading causes of death among young children despite the widespread availability of a safe and cost-effective vaccine.

The 2009-2010 measles epidemic had a profound impact on childhood morbidity and mortality in South Africa, with 2009 cases occurring in the Western Cape region of South Africa alone. Children under one year of age had the highest incidence of infection.

The burden of measles-related disease, including the impact on resources and service delivery, and the outcome of children with severe measles-related disease requiring PICU admission has been poorly reported in the last decade, particularly in the context of a country with limited PICU resources and high rate of HIV comorbidity.
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34) Impact of HIV on measles and measles immunization. [www.clinicaltrials.gov](http://www.clinicaltrials.gov)


APPENDIX A


17) Impact of HIV on measles and measles immunization. www.clinicaltrials.gov


PART C: PUBLICATION-READY MANUSCRIPT

TITLE PAGE

Title: A retrospective review of patients admitted to the pediatric intensive care unit at Red Cross War Memorial Children’s Hospital during 2010 with the clinical diagnosis of measles or measles-related complications

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Abstract

Objectives: To evaluate the outcomes of children with measles-related disease (MRD) admitted to paediatric intensive care unit (PICU) and the effect on PICU resources and elective surgery during a recent measles epidemic.

Design: Retrospective observational study. Patient demographics, severity of illness on admission, duration of PICU admission and mortality were recorded. Costs were calculated using bed days utilized and estimated daily PICU admission cost.

Setting: Multidisciplinary PICU in an academic children’s hospital in Cape Town, South Africa.

Patients: All patients admitted to PICU with MRD from January to December 2010.

Interventions: None

Measurements and Main Results: 1294 children were admitted over the study period, 58 (4.5%) with MRD (median age 7 (interquartile range, IQR 5-9) months). Pneumonia was the most common reason for admission (81%) and the main cause of mortality. Non-MRD mortality was 8.8% compared to MRD mortality of 31% ($p < 0.0001$). Standardised mortality for non-MRD was 0.7 vs. 1.7 in MRD ($p = 0.002$). HIV comorbidity and being underweight for age were associated with increased mortality.

Patients with MRD occupied 379 bed days with a median (IQR) duration of stay of days 5.5 (3.0 – 9.0) days at an estimated overall cost of R4813300 (approximately $543900). During the study period, 67 children booked for elective surgery and 87 other referrals were refused PICU admission.

Conclusions: MRD was associated with significant morbidity and mortality, and substantial strain on scarce PICU resources.
INTRODUCTION

Measles is a highly communicable disease which remains a leading cause of death among young children even though a safe and cost-effective vaccine is available (1). Because measles is highly contagious, a five percent susceptible population is sufficient to sustain periodic outbreaks in otherwise highly vaccinated populations (1). Accurate coverage of measles vaccination has been difficult to determine. A survey conducted in the Western Cape Province of South Africa in 2005 estimated that 93% of children had received the first dose of measles vaccine, but only 60% a second dose (2). The authors came to the conclusion that routine coverage in the Western Cape was too low to prevent a measles outbreak. This was proven to be correct in the 2009-2010 South African measles epidemic.

South Africa is a developing country that faces several challenges in providing adequate health care. We carry a high burden of HIV infection, poverty and malnutrition (3). HIV-infected individuals are susceptible to measles at a younger age and they also have higher rates of vaccine failure (4, 5). A study from Pakistan illustrated that complications of measles occur far more frequently in undernourished children (6). The National Institute for Communicable Diseases (NICD) survey reported a total of 18 396 proven measles cases countrywide from January 2009 to February 2011; 2009 of these cases occurred in the Western Cape (7). The first case in the Western Cape was confirmed in September 2009. Children under one year of age had the highest incidence of infection, as well as the highest mortality. At Red Cross War Memorial Children’s Hospital (RXH) alone there were a total of 552 hospital admissions for measles-related disease (MRD) from November 2009 to 31 July 2010 (8).

Intensive care unit (ICU) facilities are expensive and availability is often limited in developing countries. Determination of disease specific outcomes such as length of ICU stay and
mortality may be useful to inform cost-effective allocation of these resources. However, in developing countries, like South Africa, little data have been generated about the outcome for children admitted to paediatric intensive care units (PICU’s). Also, little recent data are available from South Africa about the impact of measles and its complications on ICU resources (9, 10, 11). This prompted our retrospective review of patients admitted to the PICU at Red Cross War Memorial Children’s Hospital (RXH) during 2010 to evaluate the outcomes of children with MRD and the effect on PICU resources during the recent measles epidemic.

**Context**

RXH is a 290-bed academic children’s hospital affiliated to the University of Cape Town in South Africa. During the measles outbreak, children that required admission were stabilized and admitted to the “short stay ward” from where they were either discharged home, transferred to another hospital (mild disease) or admitted to the medical wards or PICU (severe disease or significant co-morbid disease) (8). The PICU at RXH is a 20-bed unit that serves medical and surgical patients for both emergency and elective admissions. Approximately 1200-1300 patients are admitted per annum with the majority under 18 months of age (unpublished data).

Preventative measures taken in the unit to protect other patients and staff from acquiring measles included universal precautions, a single dose of intramuscular measles vaccine in patients older than six months of age (Rouvax, Sanofi Pasteur, France) and intramuscular measles immunoglobulin (Intragam, National Bioproducts Institute, South Africa) to all patients less than six months of age and those with severe immunosuppression. Cohorting and isolation was not possible due to the open plan structure of the PICU and the lack of dedicated isolation facilities.
METHODS

All patients admitted to the PICU from January to December 2010 with a clinical diagnosis of measles (according to the WHO clinical case definition) (12) or measles-related complications were included in a retrospective descriptive study. Clinical folders of eligible patients identified from the existing PICU database were reviewed and data recorded on a standardized data collection form (addendum A).

Recorded data were transcribed to an Excel database. Data were tested for normality using the Shapiro-Wilks W test. Comparisons of the primary and secondary outcome measures were made by means of the Mann Whitney U test for non-parametric data. The hypothesis of independence between variables was tested using Chi-Square test or Yates-corrected Chi-Square tests where cell values were less than ten. Variables identified as being associated with the binary outcome of interest (mortality) on univariate analysis were entered into a stepwise logistic regression model using an online program (http://statpages.org/logistic.html).

Associated costs were calculated using bed days utilized and estimated daily PICU cost of R12 700 (approximately $1435) per bed day (13) (PICU cost = total hospital cost x proportion of nurses that work in PICU, per annual hospital administration report).

Ethics approval was obtained from the Department of Paediatrics and Child Health Departmental Research Committee and the University of Cape Town Human Research Ethics Committee (14). All research adhered to the requirements stated in the Declaration of Helsinki (2008) (15).
RESULTS

A total of 58 patients were included in this study from the period 1 January to 31 December 2010; 26 (45%) were male. The total number of PICU admissions over the same period was 1 294; patients with MRD comprised 4.5% of this total. The majority of cases (52, 90%) were admitted from February to May 2010.

The majority of patients (45, 78%) had a normal weight for age (defined as between 3rd and 95th centiles) on admission. Data on feeding choice (breast vs. formula vs. mixed feeding) were not well documented in the files. Patient data are presented in Table 1.

Immunizations were up to date in 39 (67%) patients, while eight (14%) patients had an incomplete immunization status and the immunization status was unknown in 11 (19%) patients. Forty-two (72%) patients had not received any dose of measles vaccine by the time of their admission to ICU; nine (15.5%) patients had just one dose of the measles vaccine and only two patients (3.4%) had received both doses of the measles vaccine.

The HIV status was known in 53 (91%) patients: 33 (57%) were HIV negative, 15 (26%) were HIV exposed but negative and five (8%) were HIV infected. Of the five HIV positive patients, four were receiving highly active anti-retroviral therapy (HAART).

Fifty-four (93%) patients presented with community acquired measles, while four patients contracted measles while admitted as inpatients in a healthcare facility. There were no documented cases of PICU-acquired MRD, and no PICU staff members contracted measles. Most of the diagnoses were made on clinical grounds; laboratory confirmation (measles IgM antibodies positive) (12) could only be traced in nine cases. Measles notification was not well documented with definite notification done in only 17 (29%) cases.
The most common reason for ICU admission was pneumonia (47, 81%). Other primary admission diagnoses included septic shock (9, 16%), gastroenteritis with hypovolaemic shock (3, 5%) and laryngotracheobronchitis (LTB) (5, 9%). One patient was admitted with anaplastic large cell lymphoma with superior vena cava (SVC) obstruction. Primary diagnoses are illustrated in Figure 1 and secondary diagnoses in Figure 2. Apart from HIV exposure and/or infection, a history of prematurity was identified as the only other co-morbidity in 10 (17%) patients.

Ventilatory support was provided in 57 (98%) patients. Thirty-nine (67%) patients had conventional ventilation and 19 (32%) patients received high-frequency oscillatory ventilation (HFOV). Continuous positive airway pressure (CPAP) only was adequate in 12 (21%) patients. Four children with complications of measles had tracheostomies; one for severe croup and three for subglottic stenosis following prolonged intubation and ventilation for severe pneumonia.

Nosocomial co-infections (newly acquired pathogens identified 48 hours or more after PICU admission) were identified in 18 (31.0%) patients (table 2). Two doses of vitamin A were given in 55 (94.8%) patients. Antibiotics were prescribed in 56 (96.6%) patients and 17 (29.3%) patients received antivirals (Acyclovir and/or Ganciclovir); these drugs were prescribed at the attending physician’s discretion.

The PICU mortality (table 1) for patients with measles-related disease (MRD) was 31% (18 of 58 patients) compared to 8.8% in non-MRD patients admitted during the same period ($p < 0.0001$). The standardised mortality rate (actual/mean predicted mortality using PIM2) in patients without MRD was 0.7 compared to 1.7 in patients with MRD ($p = 0.002$).

The overall PICU mortality was 9.1% (nine of 353 (2.5%) elective admissions and 107 of 921 (11.6%) emergency admissions). The 31% mortality in those with MRD was also
significantly higher than the mortality of emergency admissions only (11.6%) during the 2010 calendar year \((p<0.0001)\). The most common cause of death in the patients with MRD was acute respiratory distress syndrome (ARDS) with progressive respiratory failure (10, 56%). The other causes of death included multi-organ failure (5, 27%) and intractable septic shock (pneumonia and Shigella dysentery with gram negative septicaemia in one patient, and pneumonia and Klebsiella septicaemia in another patient). Treatment was withdrawn in one patient that presented with ARDS and abdominal compartment syndrome with extensive bowel necrosis incompatible with life.

A greater proportion of patients with MRD who died were undernourished (< 3rd centile weight-for age), HIV infected and had worse severity of illness (PIM2) scores than those who survived (table 3). The final multiple logistic regression model identified undernutrition (adjusted odds ratio, OR 6.5; 95% confidence interval, CI, 1.6 – 27.0, \(p = 0.01\)) and PIM2 scores (adjusted OR 38.5; 95% CI 2.2 – 671.9; \(p = 0.01\)) as the only variables significantly associated with mortality in patients with MRD.

**Resource consumption**

During the study period, patients with MRD occupied a total of 379 PICU bed days, 5% of the total annual PICU bed days, at an estimated overall cost of R4813300 (approximately $543901). During the study period, 67 children booked for elective surgery and 87 other referrals were refused PICU admission. Of these, 20 children had their surgery cancelled during the height of the measles outbreak, between February and May 2010. The eventual outcomes of these patients are not known.
DISCUSSION

This paper describes the characteristics, outcome and resource utilization of children with measles or MRD admitted to PICU during a measles outbreak in South Africa. Considering that a highly effective measles vaccine has been available worldwide since 1966, it is of concern that such outbreaks continue to occur, with the majority (85%) of measles-related deaths occurring in Africa and South East Asia (16).

The median age of patients included in this study was seven months (IQR five to nine months), which is in keeping with the NICD survey (8). Seven months is below the age (nine months) at which the first dose of the measles vaccine is currently routinely administered according to the South African Expanded Programme of Immunisations (EPI) (17). That implies that these patients, on the basis of age alone, may not have had immunity to measles, since the mothers' measles antibody titres were not known and maternal antibodies decline after six months of age. In addition, 72% of patients had not received the measles vaccine by the time of their admission to ICU, 15% had one dose of the measles vaccine and only two patients (3%) had received both doses of the measles vaccine. This is in keeping with the results of a survey conducted in the Western Cape in 2005 which concluded that although 93% of children had received the first dose, only 60% received the second dose of the measles vaccine (2).

Despite two rounds of the national supplementary measles vaccination campaign for children aged six months to 15 years in April and May 2010, reports suggest that there was poor participation on the part of many parents and certain schools (18). Vaccine coverage depends strongly on the acceptance of vaccination by parents and access to the health care system. Parents may consider the potential benefits for the community (i.e. herd immunity effects and a
reduced economic burden) as less important than the individual risk from potential vaccination side-effects (19).

The age of receiving the first measles vaccine and poor compliance with the EPI is of particular concern in a population with a high burden of HIV because of the immunoparesis which occurs in association with HIV exposure and infection (20). The WHO therefore recommends that, where possible, HIV exposed and infected infants should receive a measles vaccine at six months of age in addition to the routine dose administered at nine months (1). A multicenter randomized open label trial in the US determined that the monovalent measles vaccine (Attenuvax, Merck & Co, USA) at six months of age was well tolerated and sufficiently immunogenic in HIV infected children (5). There is clearly a need for ongoing promotional campaigns in the public and private sectors, bearing in mind that a major deterrent to immunization in developing nations lies with the lack of monetary resources to purchase vaccines and with the lack of the organization and infrastructure to carry it out. Similarly, a strategy to encourage inter-country cooperation is warranted given the high levels of immigration to South Africa.

HIV infected children accounted for <10% of the affected children, but 22% of the total measles-related deaths, with four of the five HIV-infected children dying. This poor outcome in HIV- infected patients is similar to previous reports from sub-Saharan Africa (10, 21).

A Zambian study illustrated that, in regions with high HIV prevalence, measles transmission may be sustained despite high immunization coverage since HIV infected children have an early decline in maternal antibody titres, higher rates of vaccine failure and more rapid decline in measles antibodies after immunization when compared to HIV uninfected children.
(22). Data from Kenya and Zambia also suggested that HIV infection may alter how measles is transmitted. HIV infected children may not develop the characteristic measles rash and this could result in delayed diagnosis and unrecognized transmission of the measles virus. HIV infected children may also have prolonged shedding of the measles virus (22).

Although our 7% incidence of nosocomial measles acquisition was much improved from the 26% reported in the same institution in 1987 (11), it is of concern that healthcare- associated measles infection still occurs. Hospital acquisition of measles has been associated with worse outcome than community acquired infection (23), although we were unable to demonstrate this effect due to small sample size.

The measures taken to prevent nosocomial measles infection in our PICU appeared to be effective to patients and staff, as no new cases were identified as being related to PICU admission, although there was no formal documentation of the success rate of this strategy.

The diagnosis of MRD was made on clinical grounds with poor quality of laboratory confirmation and notification. This will have implications on national measles surveillance and may lead to underestimation of the extent of the problem. It may also interfere with South Africa's attempts to achieve MDG 4, i.e. reduce the under-five mortality rate by 2/3 between 1990 and 2015, as routine measles vaccination coverage has been selected as one of the indicators of progress towards achieving MDG 4 (3). Clearly there is a need for ongoing promotional vaccination campaigns in order to reach the revised target of 2020 for measles eradication (3, 24).
The most common reason for ICU admission was pneumonia in > 80% of cases, followed by septic shock, LTB and gastroenteritis with hypovolaemic shock. The diagnosis of pneumonia was primarily made according to the WHO clinical case definition with additional radiological confirmation. The vast majority of patients in our study received ventilatory support, a third of whom received HFOV. Patients receiving ventilatory support were not specifically categorized into the different types of respiratory failure and pulmonary function testing was not performed.

Previous reports from South Africa (13) showed similar presenting diagnoses to our study. Similarly, the most common reason for PICU admission and mechanical ventilation in a Californian study was pneumonia and refractory hypoxemia, although this only constituted 47% of the included patients (25). Our results differ from reports from Ireland where the major indications for hospital admission were dehydration (79%), with only 47% presenting with pneumonia or pneumonitis (26). LTB was a more common complication of MRD requiring intensive care and ventilatory support than in a study from the United States in 1990 (27). Three of the five (60%) patients with the primary diagnosis of LTB were ventilated, compared to 11% in the review by Newth et al. All three these patients had concomitant pneumonia and one required a tracheostomy for severe upper airway obstruction.

Nosocomial co-infections were identified in in a third of patients, most commonly Klebsiella pneumonia, Acinetobacter baumannii, Candida albicans and adenovirus. Adenovirus was reported as a common co-pathogen in a South African study conducted in the 1970’s (28), but co-infection has been poorly reported in other studies.

Antibiotics were mainly prescribed at the attending physician’s discretion to treat suspected bacterial pneumonia and/or sepsis. Since it is difficult to distinguish between viral and
bacterial causes of pneumonia in infants, broad spectrum antibiotics were started routinely on admission to treat the most likely bacterial organisms causing community-acquired or nosocomial pneumonia respectively. In cases where a bacterial cause were excluded or proved unlikely, the antibiotics were stopped; again at the attending physician’s discretion.

The mortality in patients with MRD of 31% was approximately three times greater than that of the general PICU population admitted over the same period, and also significantly greater than the mortality of those admitted for emergency reasons only. The most common cause of death was ARDS with progressive respiratory failure, similar to a study from an Israeli PICU in 1995 (29). Mortality rates for measles-associated pneumonia of up to 66% have been described in different settings (13, 25, 28).

Patients who died were significantly underweight for age compared to survivors. This concurs with a comparative study of measles complications in well-nourished and malnourished children conducted in Pakistan, which demonstrated that complications of measles occurred far more frequently in undernourished children (6).

The impact of PICU care for patients with MRD, as well as strategies to limit nosocomial transmission, was profound in terms of bed occupancy, cost (financial, staff and psychosocial), mortality, refusal of non-MRD patient referrals and cancellation or postponement of a number of elective surgical cases (including cardiac surgery). The outcomes of these refusals and cancellations are not known.
LIMITATIONS

This study has several limitations. Data were captured retrospectively from clinical case notes. Much of the relevant data (e.g. feeding choice, vaccination status, etc.) were poorly recorded. Few children were plotted on centile charts and height was not routinely measured, bearing in mind that weight-for-height is a more sensitive marker of malnutrition than weight-for-age. Most of the clinically diagnosed cases were not laboratory-confirmed and in the context of children with underlying problems such as HIV infection clinical identification may be inaccurate (21).

No clear distinction was made between primary viral pneumonia and secondary bacterial pneumonia or between the types of respiratory failure. These distinctions are potentially useful in planning the most appropriate ICU management protocol. It also has possible ramifications concerning antibiotic usage and development of antibiotic resistance. The study also did not address the incidence of chronic lung disease following ventilation which would lead to ongoing use of ICU, hospital and community resources. The fairly high incidence (5%) of subglottic stenosis requiring tracheostomies following prolonged intubation and ventilation was not investigated further concerning cause, contributing factors or eventual outcomes.

The resource consumption incurred by children admitted to PICU with MRD must be interpreted with caution, as this does not necessarily imply increased expenditure. If a bed were not occupied by someone with MRD, another child would have been offered PICU admission. In addition, PICU cost analyses are estimates of the true costs and do not take into account hospital management, staff or the burden on the family (in terms of lost income, transport costs etc.). The main issues relating to resource consumption are the impacts on service delivery and to patient
outcome occurring as a result of the necessary delays or cancellation of important elective surgical procedures during measles outbreaks.

CONCLUSIONS

The 2009-2010 measles outbreak was associated with significant strain on scarce PICU resources and increased mortality in patients with MRD when compared to patients with non-measles related disease. Patients under one year of age had the highest incidence of infection. That, coupled with South Africa’s large burden of HIV infection, which was associated with increased mortality, should prompt adjustment of the EPI to introduce the first dose of measles vaccine at six months of age. Countrywide attention needs to be paid to improving nutritional status, as malnutrition worsened outcome.
REFERENCES


17) Expanded Programme on Immunisation – New EPI vaccines guidelines. web.up.ac.za


**Table 1: Characteristics and outcomes of patients with MRD admitted to PICU**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (months)</strong></td>
<td>7 (5 – 9)</td>
</tr>
<tr>
<td><strong>Gender (male: female)</strong></td>
<td>26:32</td>
</tr>
<tr>
<td><strong>PIM2 score</strong></td>
<td>0.0953 (0.046 – 0.2513)</td>
</tr>
<tr>
<td><strong>Duration of ventilation (days)</strong></td>
<td>4.0 (2.0 – 8.0)</td>
</tr>
<tr>
<td><strong>Length of PICU stay (days)</strong></td>
<td>5.5 (3.0 – 9.0)</td>
</tr>
<tr>
<td><strong>Mortality n (%)</strong></td>
<td>18 (31)</td>
</tr>
</tbody>
</table>

Continuous data are median (interquartile range, IQR)
Table 2: Identified hospital-acquired co-infectious pathogens (some patients had more than one co-pathogen)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source</th>
<th>Positive blood culture n = 9</th>
<th>Tracheal aspirate/broncho-alveolar lavage (BAL) n = 20</th>
<th>Nasopharyngeal aspirate (NPA) n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
<td></td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td></td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter spp</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral (by multiplex PCR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td></td>
<td></td>
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<td>1</td>
</tr>
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</table>
Table 3: Comparison between MRD survivors and non-survivors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survived (n = 40)</th>
<th>Died (n = 18)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (months)</td>
<td>7 (5 – 9)</td>
<td>7 (5 – 9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Gender (male: female)</td>
<td>21:19</td>
<td>5:13</td>
<td>0.1</td>
</tr>
<tr>
<td>Underweight for age</td>
<td>5 (12.5)</td>
<td>8 (44.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>EPI immunizations up to date</td>
<td>28 (70)</td>
<td>11 (61)</td>
<td>0.7</td>
</tr>
<tr>
<td>HIV infected</td>
<td>1 (2.5)</td>
<td>4 (22.2)</td>
<td>0.048</td>
</tr>
<tr>
<td>HIV exposed, uninfected</td>
<td>12 (30)</td>
<td>3 (16.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>PIM2</td>
<td>0.08 (0.04 – 0.13)</td>
<td>0.17 (0.12 – 0.40)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospital-acquired measles</td>
<td>1 (2.5)</td>
<td>3 (16.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Received vitamin A</td>
<td>38 (95)</td>
<td>17 (94.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Received antibiotics</td>
<td>38 (95)</td>
<td>18 (100)</td>
<td>0.9</td>
</tr>
<tr>
<td>Received antivirals</td>
<td>11 (27.5)</td>
<td>6 (33.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Ventilated</td>
<td>37 (92.5)</td>
<td>18 (100)</td>
<td>0.9</td>
</tr>
<tr>
<td>Co-infection</td>
<td>12 (30)</td>
<td>6 (33.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>Adenovirus co-infection</td>
<td>2 (5)</td>
<td>2 (11.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>4 (2 - 7)</td>
<td>5.5 (1 – 8)</td>
<td>0.8</td>
</tr>
<tr>
<td>Length of PICU stay (days)</td>
<td>5.5 (4 – 9.5)</td>
<td>5.5 (1 – 8)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Continuous data are median values (IQR) and categorical data are n (%). Mann-Whitney U Test used for continuous data by variable mortality. EPI = Extended Program of Immunizations
FIGURES

**Figure 1: Primary admission diagnoses.**

LTB: laryngotraheobronchitis

**Figure 2: Secondary admission diagnoses**

AKI: acute kidney injury; UAO: upper airway obstruction
# PART D: SUPPORTING DOCUMENTS

## ADDENDUM A

### DATA CAPTURE INSTRUMENT

#### PATIENT DATA FORM

<table>
<thead>
<tr>
<th>Name &amp; surname:</th>
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<tbody>
<tr>
<td>DOB:</td>
<td>________________________</td>
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<tr>
<td>Folder no:</td>
<td>________________________</td>
</tr>
<tr>
<td>Sex: M / F</td>
<td>_____________</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Date of admission:</th>
<th>________________________</th>
<th>Date of discharge:</th>
<th>________________________</th>
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</table>

<table>
<thead>
<tr>
<th>Age (Months):</th>
<th>________________________</th>
<th>Home env. (region):</th>
<th>________________________</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Weight (kg):</th>
<th>________________________</th>
<th>Height (cm):</th>
<th>________________________</th>
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</table>

<table>
<thead>
<tr>
<th>PIM2:</th>
<th>________________________</th>
</tr>
</thead>
</table>
Breastfeeding:  

**EVER / NEVER**

Immunisation status:  

**COMPLETE / INCOMPLETE**

Measles vaccination:  

2 doses / 1 dose / nil

Primary admission diagnosis:

Secondary admission diagnosis:

Comorbid condition(s):

HIV status:  

uninfected / infected / exposed not infected

HAART (if indicated):  

YES / NO

Community acquired measles/ hospital acquired measles:

Laboratory confirmation of measles:  

YES / NO

Notification / case surveillance form completed:  

YES / NO

Ventilated:  

**YES / NO**  

Duration of ventilation (days):  _____
Mode of ventilation: CPAP / conventional / HFOV

Nosocomial infection: YES / NO

Type: catheter related bloodstream infections
pneumonia
UTI
other (specify)

Laboratory studies:

WCC ______________________  Hb ______________________
Platelets ____________________  CRP ______________________
PCT ______________________

Treatment: Vitamin A / antibiotics / antivirals

Outcome:
Length of PICU stay (days): __________ Length of hospital stay (days): __________

Outcome: ALIVE / DECEASED
ADDENDUM B

FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS
COMMITTEE APPROVAL LETTERS

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone (021) 406 8826 • Facsimile (021) 406 8411
e-mail: shuretha.thomas@uct.ac.za

13 June 2011

HREC REF: 273/2011

Dr S COETZEE,
PAEDIATRIC ICU
RED CROSS WAR MEMORIAL CHILDREN’S
HOSPITAL
KLIPFONTEIN ROAD, RONDEBOCH
7700

Dear Dr COETZEE,

PROJECT TITLE: A RETROSPECTIVE REVIEW OF THE 2010 MEASLES EPIDEMIC IN PATIENTS ADMITTED TO THE PAEDIATRIC ICU AT RED CROSS WAR MEMORIAL CHILDREN’S HOSPITAL WITH THE CLINICAL DIAGNOSIS OF MEASLES

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 15 June 2012

Please submit an annual progress report (FHS0168) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely,

APPROF MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Funded by the National Health and Medical Research Council. This study is a clinical trial and falls under the remit of the FHS HREC. The study is approved by the FHS HREC.

This is to confirm that the University of Cape Town Human Research Ethics Committee assures compliance with the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC)-SA, Food and Drug Administration (FDA-USA), International Conference on Harmonization Good Clinical Practice (ICH-GCP), and Declaration of Helsinki 2013.

The Human Research Ethics Committee granting the approval is in compliance with the ICH Harmonized Tripartite Guidelines E6: "Note for Guidance on Good Clinical Practice (CPMP/ICH/317/95) and FDA Code Federal Regulation Part 50, 54 and 56."