**Impact of measles epidemic at Red Cross Children's Hospital, 2009-2010:**

**a retrospective record review**

**by**

STUDENT: DAVID MARTIN LE ROUX
STUDENT NUMBER: LRXDAV004

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**Supervisor:** **Prof Brian Eley**

**Infectious Disease Unit**

**Department of Paediatrics and Child Health**

**University of Cape Town**

# DECLARATION

I, ***David Martin le Roux***, 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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Date: ……

**Index**

PO Box 159
Newlands
7725
5 August 2013

Postgraduate Committee
Faculty of Health Sciences
University of Cape Town

To Whom it may concern:

**Re: MPhil (Paediatric Infectious Diseases) submission LRXDAV004**

Included please find my MPhil mini-thesis. The study protocol, manuscript and literature review and appendices are identified in the index.

The manuscript has already been published (South African Medical Journal, September 2012). I have attached a copy of the published version as an appendix.

I trust this will meet with the approval of the committee.

Sincerely

Dr Dave le Roux
MBChB, DTM&H, Dip Obst, MPH, FCPaed(SA), MMed(Paed), Cert ID(Paed)
Dave.leRoux@uct.ac.za
082 372 8449

## Abstract

Measles is a highly contagious disease caused by measles virus. Although effective measles vaccines have been available since 1963, measles has remained a major public health problem. It remains endemic in many countries in Africa and Asia; since 2008, there have been large, sustained measles outbreaks across Western Europe and in the USA, as well as in sub- Saharan Africa. Measles mortality has increased every year since 2008.

Between April 2009 and November 2010, South Africa experienced a national measles outbreak, with more than 18 000 serologically-confirmed measles cases. The magnitude of the outbreak was most likely even greater, as many cases were diagnosed clinically without laboratory confirmation. The outbreak caused high morbidity and considerable mortality. Measles outbreaks are common in incompletely vaccinated populations; vaccine coverage in South Africa has been inadequate to prevent a measles outbreak. Outbreaks have also historically been associated with higher case fatality ratios than when measles disease is contracted by local endemic transmission. In addition, South Africa has a large population of HIV-infected children who are susceptible to measles vaccine failure, and may also be susceptible to severe complications of measles disease.

In this thesis, the impact of the 2009-2010 measles outbreak on a single paediatric hospital in Cape Town, South Africa is analysed, with description of the numbers of outpatients seen with measles, and a detailed analysis of the numbers of measles-related hospital admissions. Particular emphasis is given to the case fatality ratio observed, and the impact of age and HIV status on mortality; reasons for the high case fatality are explored.

A literature review explores the impact of HIV-infection on measles-related mortality. The apparent high case fatality described in the early reports of measles / HIV co-infection in the USA in the 1980's and 1990's is analysed; and the controversies surrounding case fatality of measles / HIV co-infection in Africa in the 1990's and early 2000's is explored. The effect of anti-retroviral therapy for HIV-infected children with measles, and areas for future research are examined.

**Research Proposal: Impact of measles epidemic at Red Cross Children's Hospital, 2009-2010: a retrospective record review**

Principal Investigator: David le Roux, Paediatric infectious disease unit, Red Cross Children's Hospital

Email: David.leRoux@uct.ac.za

Cell: 082 372 8449

Address: 4th Floor laboratory

Institute of Child Health

Red Cross Children's Hospital



**Background**

Measles outbreaks are common in incompletely vaccinated populations and are associated with high morbidity and high cost. Measles vaccine coverage in South Africa has previously been shown to be inadequate: in a survey in the Western Cape in 2005, only 60% of children received a second dose of measles vaccine[1]. A correlation between maternal HIV status and decreased probability of completing the childhood vaccination schedule has been reported from Kwa-Zulu Natal[2]. The falling measles vaccination coverage resulted in a large pool of non-immune individuals who were susceptible to measles infection. In addition, HIV-infected children do not receive adequate protective antibody either transplacentally or through breast feeding[3]. These combined factors placed South Africa at risk for a measles epidemic[1].

Since January 2009, the National Institute of Communicable Diseases has reported 17 354 confirmed cases of measles, 1879 of which occurred in the Western Cape Province[4]. About half of the cases occurred in children under 5 years. However the NICD does not provide mortality statistics or case fatality ratios, or estimates of disease severity. Measles case fatality ratios in children are reported to range from 0.1% to 30%, depending on the age and vaccination status of the child, and whether measles occurred during outbreak or endemic transmission[5, 6]. An analysis of a subset of measles patients from the 2003-2005 epidemic in South Africa, 80% of whom were under 15 years old, revealed a 6.4% case fatality ratio; 53% of vaccine-eligible patients were unvaccinated. HIV-infected patients had significantly

increased hospitalisation requirements and a trend towards increased mortality.[7] However, measles severity and outcomes have not been described in children in Cape Town.

For these reasons we decided to investigate the measles patients seen at Red Cross Children's Hospital during the current measles epidemic, and report on the proportion needing hospitalisation, the proportion of incompletely vaccinated children, the case fatality proportion and the severity of disease associated with other chronic medical conditions.

## 1) Aim

To describe the impact of the 2009-2010 measles outbreak on Red Cross Children's Hospital.

Specific objectives

1) To report the number of children with measles seen at the hospital from November 2009 until July 2010; and calculate the cost to the hospital of treating these children.
2) To describe the presentation and course of measles: age at onset, symptoms, disease severity, length of hospital stay, incidence of complications, case fatality.
3) To explore vaccine issues: how many of the measles cases were incompletely vaccinated; vaccine effectiveness in HIV-infected children; and where possible, to describe the differences in infant protection if the mother was vaccinated, unvaccinated or had had measles infection.
4) To assess the outcome of measles infection in children with background medical disease (cardiac disease, renal disease, HIV infection, chronic pulmonary disease). We will review all the deaths associated with measles and describe co-morbidities and potential modifiable factors.
5) To describe the cases of measles pneumonia: risk factors for severe pneumonia; severity of disease, ventilation requirements; incidence of secondary bacterial infections, courses of antibiotics prescribed; short term outcomes (survival) and long-term (length of hospital stay, recurrent re-admissions).

## 2) Methodology

A) Setting: Red Cross Children's Hospital
B) Study design: Retrospective folder review of all patients with proven or suspected measles infection from November 2009 to July 2010.
C) Characteristics of the study population:

*Age range*: All children seen at the Hospital will be eligible for inclusion the analysis. This will include children from a few days old to age 13, with a few teenagers with chronic medical conditions.

*Inclusion criteria*: Suspected or confirmed measles infection, based on the clinical measles definition (Appendix 1). Will include patients seen in the outpatients department, clinics and wards; and patients diagnosed at another institution and transferred to Red Cross Children's Hospital.

*Exclusion criteria*:

Suspected measles patients who were subsequently proven to have another cause for their symptoms.

Staff members, parents and other adults who were formally or informally diagnosed at Red Cross Children's Hospital but were not treated as hospital patients.

D) Recruitment and enrolment

We will derive a list of names from the hospital notification records, and correlate with hospital attendance records.

E) Ethical issues: research procedures and data collection

The study protocol will be submitted to the Research Ethics Committee of the School of Child and Adolescent Health, the administration of Red Cross Children's Hospital, and Human Research Ethics Committee of the University of Cape Town. The study will be undertaken in accordance with the Declaration of Helsinki.

Members of the research team will obtain the hospital records of measles cases; data capture sheets will contain names and folder numbers to allow researchers to check information from folders after data collection is completed. Each name/folder number will be linked to a study number; study numbers but not names will be entered onto an electronic data base for anonymous analysis and reporting. Quality control will require a random selection of 5% of the case notes be reviewed by another member of the research team or the principal investigator and accuracy of data entry corroborated.

The principal investigator will analyse the data base. Missing data will be sought in the original clinical notes. We will not seek to make contact with the patients' families to clarify outcomes or obtain missing data.

F) Data safety and monitoring

As this is a retrospective record review, we do not anticipate that there will be adverse events or need for a Data Safety Monitoring Board.

G) Statistical analysis

The abstracted data set without any personal identifiers will be stored electronically. Data will be collected and recorded into a spreadsheet (Microsoft Excel) and then analysed in Stata 10 (Statacorp, College Station, Texas).

Normally distributed continuous variables will be reported as mean (standard deviation). Non-normally distributed continuous variables will be reported as median (interquartile range). Categorical variables will be compared by t test. Risk ratios and confidence intervals will be calculated using standard formulae. Adjusted odds ratios will be modelled using logistic regression. Count outcomes will be modelled using Poisson regression.

**3) Outputs**

The data will be presented at a departmental meeting and submitted for publication. It will form the basis of an MPhil (Paediatric Infectious Diseases) subspecialist qualification for the principal investigator.

**5) Anticipated gain in scientific knowledge**

The study will contribute to the understanding of measles infection in a high HIV-prevalence area. Identification of risk factors for poor outcomes may affect future case management. Results may be generalisable to other hospitals in South Africa and across sub Saharan Africa.

**6) Description of risks and benefits**

As this is a retrospective record review, we do not anticipate any risk or harm to the study patients. There are no direct benefits to the study participants.

**5) Informed consent process**

(Not applicable)

**6) Privacy and confidentiality**

After the data has been captured, the data set will not contain any personal identifiers.

**7) Reimbursement for participation**

(Not applicable)

**8) Emergency care and insurance for research-related injuries**

(Not applicable)

## 9) References

1) Corrigall J, Coetzee D, Cameron N. S Afr Med J. 2008 Jan;98(1):41-5. *Is the Western Cape at risk of an outbreak of preventable childhood diseases? Lessons from an evaluation of routine immunisation coverage*.

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3) Scott S, Moss WJ, Cousens S, Beeler JA, Audet SA, Mugala N, Quinn TC, Griffin DE, Cutts FT. Clin Infect Dis. 2007 Dec 1;45(11):1417-24. Epub 2007 Oct 22. *The influence of HIV-1 exposure and infection on levels of passively acquired antibodies to measles virus in Zambian infants.*

4) National Institute of Communicable Diseases, www.nicd.ac.za, accessed 31 August 2010

5) Cairns KL, Nandy R, Grais RF. Emerg Themes Epidemiol. 2010 Jul 19;7(1):4. *Challenges in measuring measles case fatality ratios in settings without vital registration.*

6) Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Int J Epidemiol. 2009 Feb;38(1):192-205. *Estimates of measles case fatality ratios: a comprehensive review of community-based studies.*

7) McMorrow ML, Gebremedhin G, van den Heever J, Kezaala R, Harris BN, Nandy R, Strebel P, Jack A, Cairns KL. S Afr Med J. 2009 May;99(5):314-9. *Measles outbreak in South Africa, 2003-2005.*

## 10) Appendices

1) Measles clinical case definition:

   A history of fever AND

   Macuolpapular rash AND

   A history of ONE of the following: cough OR coryza OR conjunctivitis

2) Measles case investigation form

(Attached)

**Data collection sheet (version 3.0)**

Study title: Impact of Measles Epidemic at Red Cross Children's Hospital: 2009-2010

***Biographical information***

| | | |
|---|---|---|
| Study number | | |
| Folder number | | |
| Date of birth | | |
| Gender | MALE | FEMALE |
| Suburb / Township | | |
| mass (kg) at diagnosis | | Z-score: |

***Measles immunisation status***

| | | | |
|---|---|---|---|
| Patient has RTCH | YES | NO | UNKNOWN |
| Measles vaccine – 1st dose given | YES | NO | UNKNOWN |
| Measles vaccine – 2nd dose given | YES | NO | UNKNOWN |

***HIV infection***

| | | | | |
|---|---|---|---|---|
| Patient tested for HIV | | YES | NO | UNKNOWN |
| HIV Test | Date | | Result | |
| Rapid | | | | |
| HIV ELISA | | | | |
| HIV DNA PCR | | | | |
| HIV status | exposed | infected | uninfected | UNKNOWN |
| CD4 completed | YES | NO | UNKNOWN | |
| CD4 date | | | | |
| CD4 absolute count | | | | |
| CD4 percentage | | | | |
| On ART at time of infection | YES | NO | UNKNOWN | |
| Date of starting ART | | | | |
| Time on ART (indicate days/months) | | | | |

***Location of measles diagnosis and management***

| | |
|---|---|
| Date of measles diagnosis | |
| 1st hospital location (MOPD/Med Reg/etc.) | |
| Admission to ward to S11 / SSWE? | |
| Date of admission to S11 / SSWE | |
| Subsequent ward movements | |
| Ward | Date of admission |
| | |
| | |
| | |

***Notification and confirmation of diagnosis***

| | | |
|---|---|---|
| Was child notified? | YES | NO |
| Date of notification | | |
| Was blood sent for IgM studies | YES | NO |
| Measles IgM result | | |
| Rubella IgM result | | |

***Indication for admission***

| | |
|---|---|
| Date of admission | |
| Principal diagnosis | |
| Additional diagnoses | |
| | |
| | |
| | |

***Underlying medical condition***

| | | |
|---|---|---|
| Underlying medical condition | YES | NO |
| Specify | | |
| | | |
| | | |
| | | |

***Vitamin A administration***

| | | | |
|---|---|---|---|
| 2 doses administered | YES | NO | UNKNOWN |

***Complications during admission and outcome***

| | | |
|---|---|---|
| Complication associated with admission diagnosis:- | | |
| Respiratory failure | Septic shock | |
| Other (specify): | | |
| ICU admission required | YES | NO |
| Indication for ICU admission: | | |
| Total length of hospital admission: | | |
| Hospital outcome | Discharged | Died |
| Date of discharge / death: | | |
| Cause of death: | | |

**Part 2: Admission with Measles pneumonia**

| | |
|---|---|
| Date measles diagnosed: | …… |
| Date admitted to RXH: | |
| Admitted to ward: | |
| Transferred in from: | |

All cultures taken: (positive and negative)

| Blood Date | Result: | CSF: Date | Result | Urine: Date | Result | NPA: Date | Result | TA: Date | Result | BAL: Date | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|
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Only positive culture:

| Date | Site | Organism | Sensitive to | Resistant to | Intermediate to |
|---|---|---|---|---|---|
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Antibiotics:

| Name | Date started | Date completed |
|---|---|---|
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| | | |

Ventilation requirements

| Date | Form of ventilation | O2 Requirement | Sats |
|---|---|---|---|
| | | | |
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| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

Blood transfusions

| Date | Starting Hb | O2 Requirement | Volume of packed cells transfused | Post TF Hb |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |

Chronic illness: Readmissions

| Date | Ward | Presenting complaint | Final diagnosis |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

## MEASLES CASE INVESTIGATION FORM

EPID NUMBER:_____

Name of person completing form:_____Signature:_____

Sources of Data: Caregiver ☐ Clinician ☐ Medical records ☐ No data obtained ☐

Name of Health Facility attended:_____ Name of attending clinician:_____

Health Facility street address:_____

_____Contact number:_____

### PATIENT DETAILS

Full name: _____Gender: M ☐ F ☐ Unknown ☐

Date of birth: ____/____/____ If DOB unknown Age: ___ Unit: Days ☐ Wks ☐ Months ☐ Yrs☐; DOB and Age Unk ☐

Street address:_____

_____Town/ City:_____ Province:_____ Contact Number(s): _____

### CURRENT PRESENTATION

Presenting symptoms/signs (Tick all applicable Boxes): Rash ☐ Fever ☐ Conjunctivitis ☐ Cough ☐

Coryza/Rhinitis/runny nose ☐ Other (Specify)_____

| | |
|---|---|
| Date of onset of rash: _____/_____/_____ | Date of Presentation at the health facility: _____/_____/_____ |

Complications (Tick where applicable): None ☐ Pneumonia ☐ Otitis Media ☐ Diarrhoea ☐ Febrile seizures ☐

Laryngotracheobronchitis (Croup) ☐ Corneal Ulceration ☐ Blindness ☐Encephalitis ☐

Clinical Management: Vitamin A given: Y ☐ N ☐

Final outcome (Tick where applicable): Patient admitted to Hospital: Y ☐ N ☐ Patient Died: Y ☐ N ☐

Specimens Collected (Tick where applicable): Blood/Serum ☐ Urine ☐ Nasopharyngeal/Saliva ☐

Dried Blood Spot ☐ Date of specimen collection: _____/_____/_____

### MEDICAL AND CONTACT HISTORY

History of contact with a suspected measles case in the past 7 to 28 days: Y ☐ N ☐ Unknown ☐

History of contact with a laboratory confirmed measles case in the past 7 to 28 days: Y ☐ N ☐ Unknown ☐

History of travel in the past 7 to 28 days: Y ☐ N ☐; if yes, name of place or country travelled to _____

History of previous visit or admission to a healthcare facility in the past 7 to 28 days: Y ☐ N ☐ Unknown ☐ ;

If yes, Name of the Facility:_____ Diagnosis at the Facility:_____

Vaccination Information obtained from: Road to health card ☐ Self reported ☐ Not obtained ☐

| | |
|---|---|
| Measles vaccination received: Y ☐ N ☐ Unknown ☐ | If yes, number of doses: 1 ☐ 2 ☐ >2 ☐ Date of last measles vaccine: _____/_____/_____ |

### RESPONSE TO CASE

Case Notified: Y ☐ N ☐ Unknown ☐ Date of Notification_____/_____/_____

| Contacts follow-up | Number | | | Action Taken |
|---|---|---|---|---|
| | < 5 yrs | 5-14 yrs | >=15 yrs | |
| Household | | | | |
| School/Creche | | | | |
| Other (Specify)_____ | | | | |

Active Case Finding: Y ☐ N ☐ Number of suspected measles cases found: None ☐ or specify number_____

**NB: Complete an additional case investigation form for each suspected measles case identified**

**South African measles outbreak 2009-2010: experience of a paediatric hospital**

David M le Roux*, MBChB, DTM&H, FCPaed(SA), MMed(Paed), MPH; Stanzi M le Roux, MBChB, DCH; James J Nuttall,* MBChB, FCPaed(SA), DTM&H ; Brian S Eley,* MBChB, BSc, FCPaed(SA)

*Infectious Diseases Unit, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and University of Cape Town, South Africa

Corresponding author
Dr David M le Roux
Red Cross War Memorial Children's Hospital
Klipfontein Road
Rondebosch, 7700
Cape Town, South Africa
DrDaveleRoux@gmail.com

The authors declare they have no conflict of interest.

**Abstract**

*Introduction*

Between 2009 and 2010, South Africa experienced a major measles outbreak, with more than 18 000 confirmed cases reported to the National Institute of Communicable Diseases. We studied measles admissions during the outbreak at a paediatric hospital in Cape Town, and investigated factors associated with mortality.

*Methods*

Children presenting to Red Cross War Memorial Children's Hospital with measles between 1 November 2009 and 31 July 2010 were retrospectively identified from notification records and hospital admissions data. Multivariate logistic regression was used to investigate potential risk factors for death.

*Results*

In total, 1861 children were diagnosed with measles; 552 (30%) were admitted to hospital. The most common reason for admission was pneumonia (379, 68%) and/or diarrhoea (262, 48%). The median age at admission was 7.36 months (interquartile range (IQR) 5.0 to 10.7). The median duration of admission was 4 days (IQR 2-6); total hospital admission time was 3746 days (10.3 child-years). HIV status was known in 404 children (73%): 39/400 (14%) were HIV-infected. Eighteen children died (3% of all admissions); 15 of these (83%) were less than 1 year old. In the regression model, HIV-infection (adjusted odds ratio (aOR) 7.55, 95% confidence interval (CI) 2.27 – 25.12) and female sex (aOR 3.86, 95% CI 1.26 – 11.84) were associated with higher odds of death.

*Conclusions*

There was a large paediatric admission burden during the 2009-2010 measles outbreak in Cape Town; young children were predominantly affected. HIV-infected children had significantly higher case fatality.

## Introduction

Measles vaccination has been very effective in reducing global measles disease burden. However, outbreaks can occur when inadequate vaccination coverage allows accumulation of sufficient number of susceptible individuals in a population. The estimated level of population immunity needed to prevent measles outbreaks is about 95%.[1] South Africa introduced routine measles vaccination in 1975, and measles became a notifiable condition in 1979. In 1995, the current 2-dose strategy (routine vaccination at 9 and 18 months) was adopted. Case-based surveillance was introduced in 1998, with all suspected cases having blood or urine tested at the National Institute of Communicable Diseases (NICD).[2]

Accurate coverage of measles vaccination has been difficult to determine. In 2009, the South African Department of Health estimated national coverage with routine measles vaccine to be 99%, but the World Health Organisation (WHO) and United Nations Children's Fund (UNICEF) coverage estimates were only 65%.[3] In 2004, a survey in the Western Cape found 79% of children to be "fully vaccinated".[4] In 2005, another study estimated that 93% of children had received the first dose of measles vaccine, but only 60% a second dose.[5] The authors concluded that routine coverage in the Western Cape was too low to prevent a measles outbreak.

The last major outbreak in South Africa occurred in 1992. In July 2009, a cluster of measles cases was detected in Tshwane; in August, the outbreak spread to Johannesburg, and thereafter rapidly throughout the rest of the country. The first case in the Western Cape was confirmed in September 2009; there were 14 cases in October and by November the outbreak was well established throughout the Cape Town metropole.[6] We report the epidemiology of measles cases presenting to a single paediatric hospital in Cape Town, South Africa.

## Methods

*Setting*

Red Cross War Memorial Children's Hospital (RCWMCH) is a 290 bed level 3 academic hospital in Cape Town. During the outbreak, children with measles who needed admission were stabilised and admitted to the "short stay ward". From the short stay ward they were either discharged home, transferred to another hospital (mild disease), or admitted to the medical wards

or Intensive Care Unit (ICU) at RCWMCH (severe disease or other significant co-morbid disease).

*Study population*

All children diagnosed with measles at RCWMCH between 1 November 2009 and 31 July 2010 were retrospectively identified from paper notification records, electronic hospital admission records, and the ICU database. Folders were reviewed and patients meeting the World Health Organisation (WHO) clinical case definition were included.[7] Suspected measles cases who tested negative for measles IgM antibodies were excluded. Data were captured onto a paper form and entered into an electronic database.

Final discharge dates and readmission dates were extracted from the city-wide hospital admission computer system; this includes all the time spent in any hospital in the city.

*Measles case management and prophylaxis*

All children were managed according to written hospital protocols. In-patient management of pneumonia included intravenous ampicillin, gentamicin and cloxacillin. Vitamin A was dosed according to WHO guidelines.[7] During the outbreak, all children attending RCWMCH who did not have clinical measles were given measles prophylaxis. Children older than 6 months were given a single dose of intramuscular measles vaccine (Rouvax, Sanofi Pasteur, France); children under 6 months and children with severe immunosuppression were given an intramuscular dose of human immunoglobulin (Intragam, National Bioproducts Institute, South Africa), according to the manufacturer's instructions.

*HIV testing*

HIV testing was performed when deemed clinically appropriate by the treating clinicians. Children over the age of 18 months were considered HIV-infected if HIV antibodies were detected by ELISA (enzyme linked immunosorbent assay) testing. Results were confirmed on a second specimen with a manual ELISA (Enzygnost® Anti-HIV 1/2 Plus, Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany). Children less than 18 months of age were considered HIV-infected with positive HIV DNA PCR (Cobas Ampliprep system, Roche

Molecular Systems, Branchburg, New Jersey, USA). Positive HIV DNA PCR results were confirmed with HIV viral load testing.

*Statistical analysis*

For summary statistics, categorical data are expressed as number (percentage); continuous data are expressed as median (inter-quartile range, IQR). Median values were compared with the Wilcoxon rank-sum test. Risk ratios were calculated to compare the proportion of children who died or were re-admitted by gender and HIV status.

Factors associated with death were explored with multivariable logistic regression. We evaluated the impact of age, sex, HIV status, immunization status, evidence of vitamin A administration, the presence of a "Road to Health Card" and the weight-for-age Z-score (calculated from growth charts from Centers for Disease Control and Prevention (CDC)). Weight-for-age Z score of less than -2 was considered "moderate underweight for age"; less than -3 was considered "severe underweight for age". Variables associated with the outcome at the $\alpha$=0.1 level were included for multivariable analysis. Automated backwards and forwards step-wise model building procedures were used; potential models were compared with Akaike's Information Criteria. Collinearity was assessed with variance inflation factors. The final model chosen was most parsimonious and presented the best AIC value. A sensitivity analysis was done to examine the influence of the children with unknown HIV status. Analyses were done in Stata version 10 (Statacorp, College Station, Texas, USA). All p-values are two-tailed ($\alpha$=0.05).



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, HREC-REF number 511/2010.

**Results**

From 1 November 2009 till 31 July 2010, 1861 children with measles presented to RCWMCH.

*Outpatients:*

1309 children (70%) were treated as outpatients; most cases presented in March and April 2010 (fig 1). The median age was 8.9 months (IQR 6.1 to 30.4), table 1. Documentation of measles

vaccination status in the hospital notes was poor: of the 565 children eligible for routine measles vaccination, only 270 (48%) had vaccination status recorded, and only 68% had vitamin A administration documented in the hospital notes, table 1.

*Admissions:*

There were 552 hospital admissions; inpatients were significantly younger than children treated only as outpatients (median age 7.4 months vs. 8.9 months, Wilcoxon $p<0.0001$), table 1. Most children (357/552, 65%) were younger than 9 months, the age of routine measles vaccination, fig 2. At least 379 (63%) children presented with pneumonia, 262 (47%) with severe diarrhoea and 163 (30%) with both. Other reasons for admission included croup (37, 7%), and suspected meningitis (2, 0.4%). Vaccination status was recorded in the hospital notes in 92/195 (47%) children older than 9 months; only 40/92 (45%) had had any measles vaccine documented in the hospital notes, fig 2. During the study period, venous blood for serological testing was sent from 102 children admitted with suspected measles. Ninety-six (17%) had detectable measles IgM antibodies; 4 specimens were invalid or insufficient. Only 2 children with clinically-suspected measles were confirmed measles IgM negative; both children had detectable rubella IgM antibodies, and were excluded from this analysis.

Four hundred and four of the admitted children (73%) had known HIV status: 39/404 (10%) children were HIV-infected, of whom 20/39 (51%) had been on anti-retroviral therapy (ART) for more than 3 months. All HIV-infected children with severe measles subsequently commenced ART. Only 3/23 (14%) HIV-infected, vaccine-eligible children had documentation of any measles vaccination.

*Deaths and complications*

Eighteen children died (3% of all admissions); 13 of these (72%) were less than 1 year old. Eleven (61%) deaths were due to respiratory failure; other causes included septic shock with multi-organ failure (4 children, 22%) and cerebral ischaemia after cardio-respiratory arrest (2 children, 11%). One child died from massive bowel ischaemia and necrosis.

Seven of 39 (18%) HIV-infected children died, versus 11/365 (3%) known HIV-uninfected children. Case fatality was higher among girls: 5% of girls died versus 1.7% of boys, table 2. In multivariable logistic regression adjusted for age and weight-for-age, HIV infection and gender remained strong predictors of mortality, table 3. Two of the 7 (29%) HIV-infected children who died had received ART for at least 3 months.

During the study period, 4 children with complications of measles required tracheostomies (Sr Jane Booth, personal communication). One child was referred with severe croup; three children developed upper airway damage following prolonged intubation and ventilation for severe pneumonia. All 4 entered the RCWMCH home tracheostomy program, and were discharged home within 2 months of their admission. However they had recurrent re-admissions with respiratory infections. By March 2012, three children had been successfully decannulated, and one remains with a tracheostomy.

*Length of stay and readmissions*

The median duration of admission was 4 days (IQR 2-6 days). HIV-infected children were admitted for longer (median 6 days, IQR 4-14 days) than HIV-uninfected children (median 3 days, IQR 2-5 days; Wilcoxon p=0.0007).

Among survivors, boys were more likely to need readmission than girls: 53/287 (18%) of boys were readmitted, versus 19/247 (8%) of girls (risk ratio (RR) for readmission 2.40 (95% CI 1.46 – 3.94, p=0.0003)). Moderate or severe underweight for age (weight for age Z-score less than -2) was also strongly associated with readmission: of 531 surviving children with known weight-for-age, 26/113 (23%) children who were moderately or severely underweight for age were readmitted, versus 46/418 (11%) of children who were not underweight for age, RR 2.09 (95% 1.36 - 3.23, p=0.0009). HIV-infected children were more likely to be readmitted; 28% (9/32) HIV-infected children were readmitted versus 12% (44/354) HIV-uninfected children (RR 2.26, 95% CI 1.22 - 4.20, p=0.01).

Total primary hospital admission time was 3746 days (10.3 child-years). Of the 534 surviving children, 72 (13%) were readmitted within 90 days. Twenty-four of these children (24/534, 4%

of all the survivors) were readmitted a third time within 90 days of their first admission. The total time spent in hospital, including the primary admission and subsequent readmissions within 3 months of discharge, was 4477 days (12.3 child-years). This constitutes 6.6% of total in-patient days at RCWMCH during the study period.

**Discussion:**

Between April 2009 and November 2010, South Africa experienced a national measles outbreak, with 18311 serologically confirmed measles cases. Almost a quarter of these cases were infants younger than 9 months.[8] The magnitude of the outbreak was most likely even greater, as many cases were diagnosed clinically: in our institution, only 96/552 (17%) measles admissions were laboratory confirmed.

At RCWMCH, the main burden of disease, both in terms of hospitalisations and mortality, was in infants under 1 year; there was an especially high burden in infants younger than 6 months. There are several reasons why the very young were so severely affected. Children become susceptible to measles infection once maternally-derived transplacental antibody levels are below a protective threshold. Vaccinated women transfer less antibody than mothers whose immunity followed wild-type measles infection. In Belgium, babies of vaccinated women received 3-times lower titre of measles-specific antibodies than babies born to women with immunity due to natural measles infection.[9] The antibodies are also lost more quickly: the median time to loss of immunity was 0.97 months for babies born to vaccinated women versus 3.78 months for babies born to women with previous measles infection.[9]

In Cape Town, there has been little circulating measles virus since the 1992 outbreak; most women of childbearing age have not had natural measles infection. Since its inception in 1975, the coverage of the measles immunization program has been too low; many women have never been vaccinated. Their babies received no measles-specific antibodies, rendering them susceptible to measles infection from a very young age.

Case fatality of measles can range from 0.1% in developed countries to 30% in outbreaks among refugee populations.. It is influenced by age, intensity of exposure to measles virus, nutritional

status, vaccination status, immune deficiency, vitamin A administration, and access to appropriate case management.[10] During this outbreak, case fatality among inpatients at RCWMCH was 3% (18 deaths out of 552 admissions). Low weight-for-age Z-score was strongly associated with increased mortality, with 35% increased odds of death for every standard deviation below the expected weight for age. Furthermore, among survivors, low weight for age Z-score doubled the risk of readmission. The finding of similar measles incidence among boys and girls, but with increased mortality among girls has previously been described,[11] but the biological mechanism is not well understood.

We observed increased case fatality among inpatients with HIV-infection: these children had an 18% case fatality ratio, and a 7-fold higher odds of death compared to HIV uninfected children, despite half of them being established on anti-retroviral therapy. This is higher than what has previously been reported in areas with high HIV prevalence. In the 2003-2005 measles outbreak in Johannesburg, 14% of known HIV-infected children died; they had a 3.3 times increased risk of death compared to HIV-uninfected children.[12] In a 6 year study in Zambia, case fatality among HIV-infected children was 12%, with 2.5 times increased odds of death compared to HIV-uninfected children.[13] The higher case fatality in this study may reflect a selection bias for disease severity: children admitted to RCWMCH had more severe disease than children treated as outpatients or in other facilities in the city.

There are several reasons why HIV-infected children have a more severe clinical course than HIV-uninfected children. HIV-infected children have deficient cellular and humoral immunity, as well as impaired innate immune responses.[14] Despite commencing ART, HIV-infected children had double the risk of re-admission compared to HIV-uninfected children. This may reflect the combined immune-suppressive effect of acute measles infection in an already-compromised individual. HIV-infected children have suboptimal responses to measles vaccination. Vaccination, even if not fully protective against measles infection, can attenuate severity of disease.[10] In HIV-uninfected children, response to measles vaccination is age-dependant, with better antibody responses in older children: at 9 months, about 90% will develop protective antibody levels (interquartile range 82 – 95%); at 12 months, 99% will develop protective levels after a single dose of measles vaccine, (interquartile range 93 – 100%).[7]

However, in HIV-infected children, the response to vaccination does not improve with age. A meta-analysis of 26 studies of vaccine responses in HIV-infected children at different ages showed highly variable responses, but no trend towards improved seroconversion among older children. The efficacy of a single dose of measles vaccine whether given at 6, 9 or 12 months was about 59% (95% CI 46-71%).[15] These studies only reported attainment of protective antibody levels, and did not take into account T cell-mediated immunity, effectiveness of protection from clinical disease, or the effect of commencing ART. However, in a retrospective analysis of the 2003-2005 measles outbreak in Johannesburg, effectiveness of measles vaccine in preventing clinical disease among HIV-infected children was calculated at 63%.[12] Infants born to HIV-infected mothers who are themselves uninfected (HIV-exposed, but uninfected) also have increased susceptibility to measles infection. HIV-exposed infants have lower levels of maternal antibody, and protective antibody is lost earlier than in HIV unexposed infants.[16]

Among the children admitted to hospital, there were 69 possible "vaccine failures" – children with record of at least 1 dose of measles vaccine, who developed severe clinical disease requiring admission. There are a number of possible explanations for these vaccine failures. When vaccinations were documented, the admitting clinician noted whether measles vaccine had been given, but not the date of administration. It was not possible to determine retrospectively the age at vaccination or time from vaccination till clinical disease. All children over 6 months of age received measles vaccine if they attended hospital, and there were two nationwide mass vaccination campaigns (12-23 April and 24-28 May 2010). However, vaccination of young children is known to be less effective than of children over 1 year of age.[7] Some children may already have been infected with measles, but were vaccinated while in the incubation period. All children under 6 months of age seen at the hospital who did not have measles were given measles immune globulin. If these children were subsequently vaccinated, the immune globulin could impair vaccine effectiveness for up to 9 months.[17] If they developed clinical measles despite having had a vaccine dose recorded in their Road to Health Card, they would be considered vaccine failures.

There are several limitations to this study. As the data was captured retrospectively from clinical case notes, much data had not been recorded: vaccine status was very poorly recorded, so we

were not able to explore many of the possible vaccine failures. Weight-for-height is a better marker of malnutrition than weight-for-age, but very few children had their height measured. Some children with low weight-for-age Z-scores may have been born pre-term; it may be a marker of low birth weight or pre-term delivery, not adequacy of post-natal nutrition. Most of the clinically-diagnosed cases were not laboratory-confirmed. Dermatologists reviewing children admitted with severe measles at another hospital in Cape Town during the epidemic found a high correlation between clinically-suspected measles and laboratory-confirmed measles. However, this may not apply to clinical diagnosis of mild disease in outpatients.[18]

In conclusion, the 2009-2010 measles outbreak was associated with a large case load, and high morbidity and mortality at Red Cross War Memorial Children's Hospital. Over 65% of the admissions were for children aged less than 9 months. Measles is a preventable disease, given sufficient political will for the interruption of measles transmission. We urgently need to improve vaccine coverage, and target supplementary immunization activities to under-serviced communities. HIV-infected children had significantly higher case fatality and risk of re-admission. Prevention of vertical transmission of HIV is a national priority; coverage of these programs must be extended, and early infant HIV diagnosis and treatment should be improved.

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Addendum for MPhil Thesis (Not included in published manuscript)

1) Calculation of total costs to the hospital of the measles epidemic was one of the research objectives; this was omitted from the published manuscript due to word-count limits. Total hospital costs for the study period were obtained from the hospital finance department. The average cost per day for an in-patient was calculated at about R2912 per day. The approximate cost to the hospital of all the measles admissions was R14,606,596. The 1309 measles cases who were seen as outpatients constituted 0.97% of all outpatient visits over the study period; the cost to the hospital was calculated as R1,311,876. The calculated costs of the outpatient visits is an under-estimate, as each child with measles was counted once irrespective of how many times they attended as outpatients. The total cost to the hospital of inpatient days and outpatient visits was estimated at R15,918,473.
2) Analysis of measles pneumonia was initially one of the research objectives. However, it soon emerged that one of the ICU fellows was analysing the measles pneumonia cases who were admitted to the Red Cross War Memorial Children's Hospital ICU. As her project included risk factors, ventilatory requirements and complications of measles pneumonia in ICU, in my analysis I did not explore the measles pneumonia aspect in great depth.

Table 1: Characteristics of children with measles treated as outpatients and admitted to hospital

| | Outpatients n=1309 | Inpatients n=552 | Total N=1861 |
|---|---|---|---|
| Age: months: median (IQR) | 8.9 (6.1 – 30.4) | 7.36 (5.0 – 10.7) | 8.3 (5.7 – 21.9) |
| Eligible for routine vaccination (>9 months) | 565/1309 (43%) | 195/552 (35%) | 760/1861 (41%) |
| Vaccination status documented in hospital notes | 270/565 (48%) | 92/195 (47%) | 362/760 (48%) |
| At least 1 dose of measles vaccine documented in hospital notes | 125/270 (46%) | 40/92 (45%) | 165/362 (46%) |
| Vitamin A: | | | |
| Given | 895 (68%) | 522(95%) | 1447 (78%) |
| Not documented in hospital notes | 414 (32%) | 30 (5%) | 444 (22%) |
| Boys | 610 (47%) | 292 (53%) | 902 (48%) |
| Girls | 526 (40%) | 260 (47%) | 786 (42%) |
| Unknown | 174 (12%) | | 174 (9%) |
| HIV status | | | |
| Known HIV status | | 404/552 (73%) | |
| HIV uninfected | | 369/404 (90%) | |
| HIV infected | | 39/404 (10%) | |
| On ART | | 20/39 (51%) | |
| Weight for age Z score (IQR) | | -0.76 (-1.73 – 0.24) | |
| Road to Health Card seen | | | |
| Yes | | 323 (58%) | |
| No | | 68 (12%) | |
| Not documented | | 161 (30%) | |
| Notified | | | |
| Yes | | 382 (69%) | |
| No | | 139 (25%) | |
| Not documented | | 31 (6%) | |
| Confirmed cases (IgM) | | 96/552 (17%) | |
| Median length of stay: days (IQR) | | 4 (2 – 6) | |
| Outcome: | | | |
| Died | | 18 (3%) | |
| Discharged home | | 354 (64%) | |
| Transferred out | | 179 (33%) | |
| Number readmitted (<30 days) | | 72/534 (13%) | |

IQR: Inter quartile range
ART: Anti retroviral therapy

Table 2: Deaths by sex, age, HIV status and vaccination status

| | Total deaths / Total children (%) |
|---|---|
| Age | |
| < 9months | 12/357 (3.4%) |
| >9 months | 6/195 (3.1%) |
| Sex | |
| Boys | 5/292 (1.7%) |
| Girls | 13/260 (5.0%) |
| HIV status | |
| HIV-infected | 7/39 (18.0%) |
| HIV uninfected | 11/365 (3.0%) |
| Unknown | 0/148 |
| Vaccination status | |
| Any measles vaccination | 1/93 (1.1%) |
| Never vaccinated | 11/215 (5.1%) |
| Unknown | 6/244 (2.5%) |
| Total | 18/552 (3.2%) |

Table 3: Odds ratios (unadjusted and adjusted) of death

| | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
|---|---|---|---|---|
| Weight for age Z-score | 0.70 (0.56 – 0.88) | 0.002 | 0.65 (0.47 – 0.91) | 0.012 |
| Sex: | | | | |
| Boys | 1 | | 1 | |
| Girls | 3.02 (1.06 – 8.59) | 0.038 | 3.86 (1.26 – 11.84) | 0.018 |
| HIV status: | | | | |
| HIV uninfected | 1 | | 1 | |
| HIV infected | 7.04 (2.55 – 19.41) | <0.0001 | 7.55 (2.27 – 25.12) | 0.001 |

*Adjusted for age and weight-for-age Z score

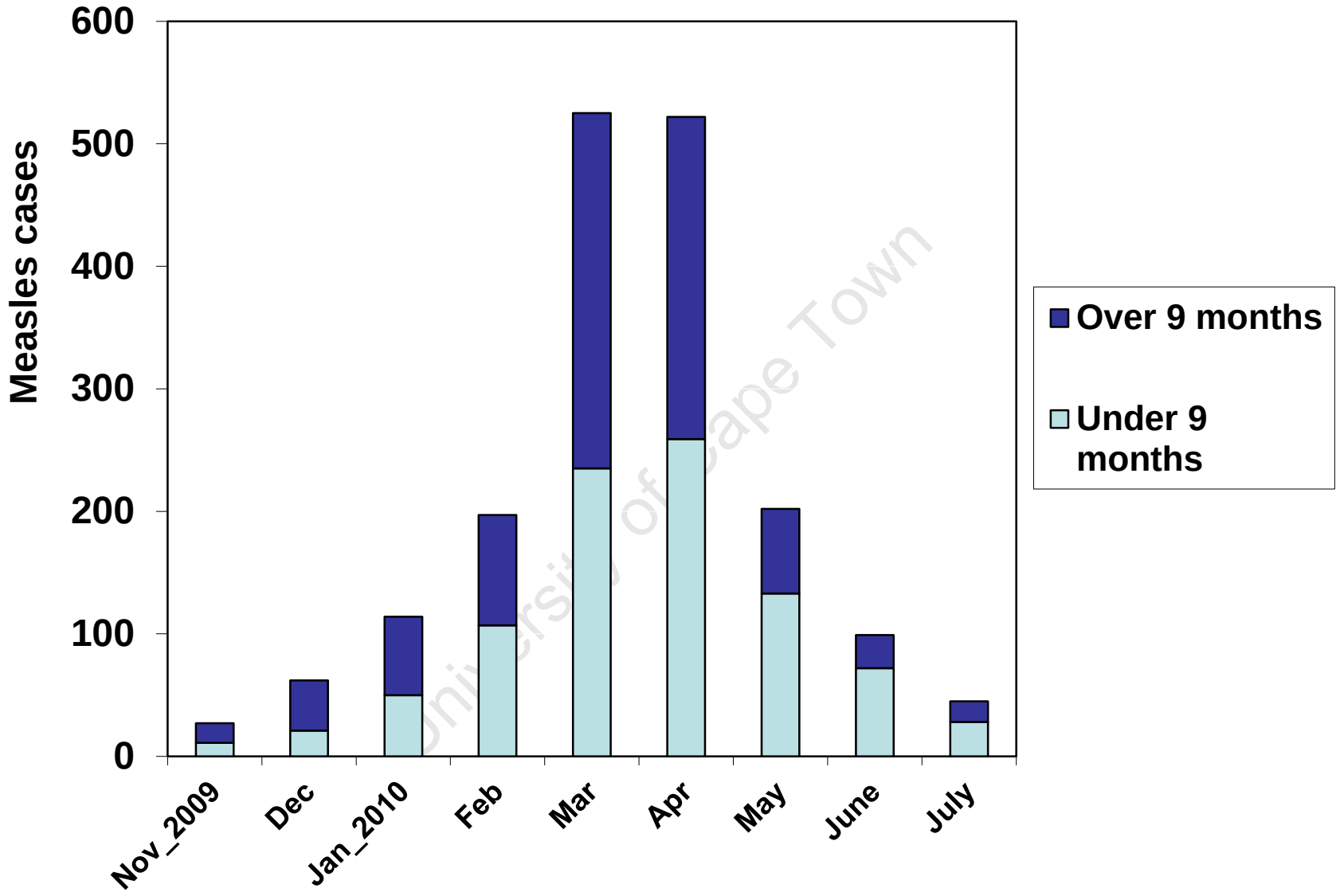


Figure 1: Measles cases by month

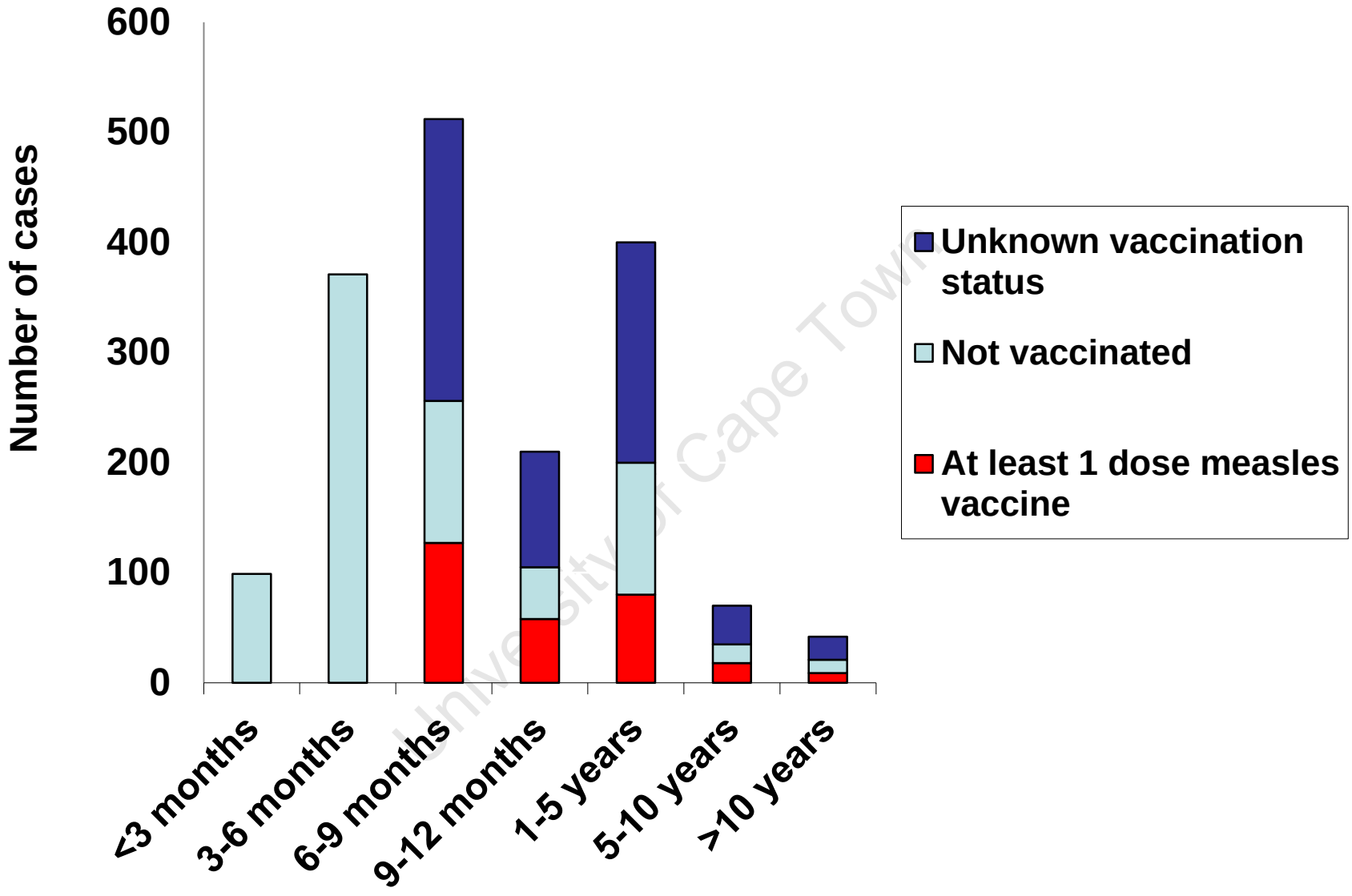


Fig 2: Number of measles cases: by age and vaccine status

**Measles case fatality comparing HIV-infected to HIV-uninfected children in pre- and post-anti-retroviral therapy eras: a literature review**

## Introduction

Measles is a highly contagious disease caused by measles virus. Effective measles vaccines, in use since 1963, have led to massive decreases in global measles morbidity and mortality.[1] However, despite improvements in measles vaccine coverage, measles has remained a major public health problem. Globally, nearly 120 000 children under 5 years died of measles in 2008; measles caused 1% of child deaths under 5 years in Africa and 3% of child deaths under 5 years in Asia.[2] Since 2008, there have been large, sustained measles outbreaks across Western Europe and in the USA, as well as large outbreaks in sub-Saharan Africa; measles mortality has increased every year since 2008.[3]

Measles disease has a highly variable case fatality ratio (CFR). Although measles deaths in industrialised countries are rare, the World Health Organisation estimates case fatality ratios in developing countries to be between 5 and 10%.[1] Other factors which are known to affect case fatality are age, intensity of exposure to infection (which is primarily associated with over-crowding), measles immunization status, malnutrition, vitamin A deficiency and immune deficiency. Due to clustering of risk factors, measles outbreaks among refugee populations can have case fatality of up to 30%.[4]

Higher case fatality ratios, along with increased severity of disease, were described among HIV/measles co-infected adults and children in the USA during the pre-anti-retroviral therapy (ART) era.[5] However, some of the early reports of case fatality ratios of measles in HIV-infected children in sub-Saharan Africa provided contradictory results, and it was hypothesized that the impact of HIV infection on measles case fatality was less marked in African children than what was observed in the USA.[5, 6] The relative risk of death from measles in an HIV-infected child compared to an HIV-uninfected child has not been quantified.

Since the advent and large-scale roll-out of ART, much attention has been given to the safety and effectiveness of measles vaccination in HIV-infected children. A large meta-analysis reported that measles vaccination in HIV-infected children is safe and rarely associated with adverse complications. However, vaccination in HIV-infected children is less effective: children have lower seroconversion rates than uninfected children, and are more

susceptible to measles vaccine failure.[7] The potential benefits of measles re-vaccination once immune reconstitution has occurred is currently being explored.[8] The independent effect of ART on measles case fatality ratio without revaccination has not been examined.

**Objectives**

This literature review addresses the case-fatality ratio of measles infection in HIV-infected children compared to HIV-uninfected children; and examines the evidence for reduction of measles-specific case-fatality ratio in HIV-infected children who are receiving ART.

**Methods**

*Information sources and search strategy*

The literature search was limited to English-language articles in MEDLINE (www.ncbi.nlm.nih.gov) and was performed on 15 January 2013. Results were limited to humans. The following search string was used:

(measles hiv) AND ((child OR children OR pediatric)) AND ("death" OR "case fatality" OR "mortality"))

**Eligibility criteria**

"Children" were defined as those less than 18 years old. Review articles or articles presenting a modelling exercise which did not present new cases were excluded. Articles that did not report any deaths, any HIV-infected children, or where it was specifically mentioned that no measles cases had occurred were also excluded. Letters, comments, guidelines and treatment protocols were excluded. When articles reported sub-analyses or interim analyses of a larger cohort, only one of the articles reporting results from that cohort was used. Individual case reports of atypical measles disease or unusual severity of disease in a single HIV-infected child were provisionally included; once it could be established that the subject of the original case report was subsequently included in a case series of HIV-infected children, then the case series was included and the case report excluded. For each case series, the total number of children was ascertained, as well as the number of new cases for analysis. Where the same patients were described in more than 1 case series, only the original description was included; subsequent references to the same child were not included in the total to prevent "double counting" of individuals. If there were

no deaths due to measles, or if the case fatality ratio of HIV-infected children was not presented separately from the overall case fatality ratio, then the article was excluded. Reference lists of all full text articles were reviewed and screened for other possible articles. Conference abstracts, grey literature and unpublished reports were not included. A single reviewer evaluated all retrieved articles by title, abstract or full text.

**Data collection and analysis**

As the intention was to get a broad overview of the topic, a range of article formats were accepted. Data was captured onto structured data capture forms. Information on study type, sample size, outcomes and loss to follow-up were noted. Case fatality ratios (CFR) were calculated manually; relative risks (RR) and 95% confidence intervals (95% CI) were calculated for case fatality using the "csi" Stata command (Statacorp, College Station, TX, USA). As the articles reported data from very different clinical scenarios, and included case series, cohort studies and opportunistic samples of hospital attenders or hospital admissions, it was difficult to exclude heterogeneity; no attempt was made to perform meta-analysis.

**Quality criteria and case definitions**

Unless the original article distinguished probable from confirmed measles infection, no distinction was made in this analysis. As serological diagnosis in HIV-infected children is often complicated by lack of robust immune response,[9] all measles cases that were included by the original authors were included, even if measles antibodies were not detected.

As far as possible, diagnosis of HIV infection was based on either virological evidence of HIV infection (DNA PCR or RNA viral load) or the persistent presence of HIV antibodies. For most studies, the cut-off age for persistent antibody presence could be set at 18 months; where the case fatality data was not stratified at 18 months, but the authors had presented grouped data at 15 months, then the author's cut-off of 15 months was used. Children below this age who had detectable HIV antibodies but without virological confirmation of infection were considered "Indeterminate HIV status". In these situations, the numbers of children with indeterminate status and the numbers who were untested were added together and regarded as "Unknown HIV status". Case fatality ratios for the confirmed HIV-infected and confirmed HIV-uninfected children were presented separately.

## Results

*Description of included studies*

The search strategy yielded 89 potentially relevant articles, figure 1. Most ineligible articles were excluded on the basis of information contained in the title or abstract. Twenty-nine articles were retrieved and reviewed in full text. Eleven articles from the Medline search were included for analysis; only 1 additional article was identified from the reference lists.

The search strategy yielded 3 case series of HIV-infected children in the USA in the 1980's and 1990's, and 2 literature reviews of case reports and case series. These five papers report 6 deaths among the 19 HIV-infected children identified, case fatality ratio (CFR) 33%, table 1.

Three retrospective reviews of measles cases in African children were identified. Two were hospital based, and recorded HIV / measles case fatality ratio among inpatients;[10, 11] the other was community-based, and identified ambulatory and hospitalised measles cases from public health notification records,[12] table 2. Three prospective studies of children hospitalised with measles were identified: two in Zambia[13, 14] and one in Zaire.[6] Another article that was identified in the search strategy[9] was excluded from the final selection for analysis as it contained interim data on the all the patients included in a later report.[13]

Only one description of a birth cohort was identified that presented measles case fatality ratio stratified by HIV status.[15] This study was part of the long term follow-up of a perinatal HIV transmission study in Nairobi, Kenya; 109 infants born to HIV-infected women and 194 control infants (born to HIV-uninfected women) were enrolled and followed for up to 3 years. However, with only 26 measles cases and 2 measles-related deaths, the comparison of case fatality is inconclusive. One of the deaths occurred in an HIV-exposed child who had clinical stigmata of HIV disease but died before confirmatory testing; the child is listed in table 2 as being of "indeterminate status".

In all 7 reports of HIV-infected children in Africa it was possible to calculate the CFR of HIV / measles co-infection; it ranged from 0%[15] to 57%[6] with a median of 18%. However, due to heterogeneity of data and study designs it was not possible to calculate a meaningful summary statistic of the CFR across the studies. From 5 of the reports it was possible to calculate a relative risk of death due to measles comparing HIV-infected and HIV-uninfected children. This ranged from 2.03 to 4.69 times increased risk of death. Two of the studies

had reported adjusted odds ratios acquired from multivariable logistic regression; these ranged from 2.5 times to 7.55 times increased odds of death.

Only 1 study reported whether or not the HIV-infected children were receiving anti-retroviral therapy.[11] Twenty of the 39 HIV-infected children (51%) had received ART for more than 3 months at the time of measles diagnosis; 2 out of 7 (29%) of HIV-infected children who died were receiving ART. Thus the CFR of children receiving ART was 2 of 20 (10%) versus 5 of 19 (26%) for children not receiving ART. This suggests a 38% reduction in the risk of death for children established on ART for more than 3 months, although the results are not statistically significant due to low sample size (RR 0.38, 95% CI 0.08 – 1.73).

**Discussion**

This literature review synthesises and organises the published evidence about the case fatality ratio in HIV-infected children with measles. Early case reports from the USA during the 1980's and 1990's described very high case fatality ratios of up to 50%.[5, 16-19] These reports contributed to the early understanding of the clinical impact of paediatric HIV disease, and illustrated the potential severity of measles / HIV co-infection. However, as the prevalence of paediatric HIV was too low in the USA, and measles cases were limited to outbreak scenarios it was not possible to accurately estimate the true case fatality at a population level.

Some authors suggested that the effect of HIV infection on measles case fatality in Africa may not be as pronounced as in the West.[5, 13] In 1999 Moss et al reported high measles case fatality ratios in the USA, and a high proportion of HIV-infections among children who died of measles in Puerto Rico. However the same paper stated that "the data comparing the severity of measles in HIV-infected and uninfected children in developing countries are less consistent".[5] The two studies that were quoted are included in this analysis.[6, 14] Sension and colleagues described 314 children with measles under the age of 5 years admitted to 2 hospitals in Kinshasa, Zaire. They reported that "no difference in the overall case fatality between HIV-seropositive and seronegative children was observed."[6] In the original analysis, all the HIV-exposed but uninfected infants and young children (who still had detectable maternal antibodies) were analysed together with the older children with confirmed HIV infection. When the case fatality of children under 15 months old (indeterminate HIV status) was calculated separately from the case fatality of children older than 15 months (confirmed HIV-infected) and HIV-uninfected children, the HIV-infected

children had a statistically significant 2-fold increased relative risk of death compared to the confirmed uninfected children (RR 2.03, 95% CI 1.04 – 3.96)

The second article[14] that was quoted by Moss in 1999 shows an even stronger effect of HIV-infection on case fatality: in this study, HIV-infected children had a highly significant 3-fold increased relative risk of death compared to confirmed HIV-uninfected children (RR 3.28, 95% CI 3.46 – 12.06). In this paper, the authors placed emphasis on the gender difference in measles mortality, and how this is influenced by vaccination. The data was presented stratified by age, gender, HIV antibody status and vaccination status. The 356 patients were divided into 24 mutually-exclusive categories. This complex means of presenting the data allows for multiple comparisons, but did not accentuate the independent effect of HIV-infection across all age groups, gender and vaccination groups.

The largest study to prospectively investigate hospitalised measles case fatality analysed 1227 children with confirmed measles and known HIV status who were admitted at the University Teaching Hospital in Lusaka, Zambia in the five and half years between January 1998 and July 2003.[13] In this study, misclassification was minimised by confirming all suspected measles cases serologically, and confirming HIV status on all participants with RNA viral load assessment. There were 189 deaths, overall CFR 5.5%. A significant 2.5 times increased odds of death for HIV-infected children compared to uninfected children was reported, after adjusting for the effect of age, sex, vaccination status, maternal education, and the presence of a desquamating rash. It is interesting that when the interim results of this study were analysed after two and half years of recruitment (from January 1998 until October 2000)[9] there had been 23 deaths among 546 children with known HIV status (CFR 4.2%) However at this stage, there was no statistical difference between HIV-infected (CFR 5.4%) and uninfected (CFR 4.0%) children, (RR 1.35, 95% CI 0.52 – 3.55). The authors did not discuss the surprising increase in CFR among the HIV-infected children during the latter three years. Of the 681 children enrolled after October 2000, there were 45 deaths (CFR 6.6%); but the deaths were disproportionately distributed among HIV-infected children: 18 of the 96 HIV-infected children enrolled after October 2000 died (CFR 19 %) compared to 27 of the 585 HIV-uninfected children (CFR 4.6%)

**Potential for bias and confounding**

*Disease severity*

In the early days of the HIV epidemic, only the most severe or dramatic measles cases would have been published as case reports, whereas mild disease or typical disease progression would not have attracted the same attention. Therefore early case report-based CFRs of up to 50% are probably overestimations of the true CFRs at that time, as the denominator would be under-estimated as mild cases would not be included. The same would apply to the calculated overall case fatality ratio of 33% among all the published cases as summarised in table 1.[5, 16-18]

In the most recent South African measles outbreak, the children with severe disease were more likely to be intensively investigated: every child who died or was admitted to ICU was tested for HIV, but 27% of the hospitalised children with mild / moderate disease were not tested.[11] Thus the case fatality ratio of 18% of HIV-infected inpatients may be an overestimate, as some of the untested children may have been HIV-infected, resulting in an underestimated denominator. Similarly, the 50% HIV-associated case fatality seen in the isolation and infectious disease wards in Durban hospitals[10] contrasts starkly with the overall measles case fatality of 7.8%, and reflects that HIV was probably under-diagnosed in the less severe measles cases (only 98 of 11 077 (0.009%) of children were tested for HIV).

*Study population*

Hospital-based studies of inpatients only describe the most severe end of the clinical spectrum of measles disease. It is not possible to accurately estimate the overall case fatality of measles /HIV co-infection without knowing the numbers of children who had mild disease and were never hospitalised. As discussed above, the birth cohort from the Kenyan perinatal HIV transmission study gives a good idea of the population-based incidence of measles, but had too few measles cases for meaningful interpretation.[15] In Cape Town between 2009 and 2010, less than 30% of the children diagnosed with measles were hospitalised.[11] The case fatality reported for the hospitalised cases (18/552, 3.0%) goes down to less than 1% if ambulatory patients are included in the denominator; however HIV status was not available for the outpatients. The only study that attempted to calculate measles/HIV CFR in a community-based setting at a district or regional level was the case-tracing study based on measles notifications to the health department in Johannesburg,

South Africa.[12] Measles cases notified from July 2004 were traced, but the field assessments and home visits of this study were performed in May and June 2005, up to 11 months after the notification. Only 31% of notified measles cases or their families could be found and interviewed. This is the only estimate available of community-based measles / HIV case fatality; however with so much missing data, possible differential loss to follow-up and the potential for inaccurate recall, both selection and information biases may affect the reliability of the estimate.

*Measles case definition*

The clinical definition of measles infection consistently included fever, cough, coryza and conjunctivitis. The duration of the rash that was required to meet the clinical case definition for a particular study ranged from 3 to 7 days; one study included the distribution of the rash (starting on the head and shoulders, then spreading distally over the next 48 hours.[15] As the exanthem of measles in HIV-infected children can be variable or absent, it is possible that some HIV-infected children with mild disease may not have been included in the case definition. If mild cases were excluded from the denominator, then the case fatality proportion may be falsely elevated. In addition, HIV-infected children may present with severe measles pneumonitis without skin rash; these children would be diagnosed with severe community-acquired pneumonia unless measles-specific viral studies were requested. Thus, some HIV-infected children with severe measles disease may not be included in the numerator as the measles infection was not clinically obvious.

*Timing of measles-related deaths*

Most studies did not specify when death had to occur to be considered “measles related”; the stated range was from 14 days after the onset of the rash[14] to within 30 days after first hospitalisation.[11] As measles infection causes profound immune suppression, can cause malnutrition and may involve hospitalisation and the risk of other nosocomial infections, it is possible that an illness episode that begins with measles infection may ultimately prove fatal, but the process could take several weeks. It is possible that more children died after measles infection than are captured in this data, and that the calculated case fatality ratios actually under-estimate the true impact of measles infection in HIV-infected children.

*Publication / language bias*

As only English titles were reviewed, it is possible that case reports or case series from South America or Central and West Africa may not have been included. It is striking that no reports from Asia were detected in the Medline search string or in the reference lists of the included articles. Thus the included cases only reflect the cases identified in Africa and the USA. However, sub-Saharan Africa has the largest total number of paediatric HIV cases, and the articles in this review may be an appropriate reflection of the global measles / HIV disease burden.

**Conclusion**

This literature review has organized the published literature regarding the case fatality of measles disease in HIV-infected children over 25 years and across 2 continents. There were not enough good quality population-based studies to accurately determine measles / HIV case fatality among ambulatory children; and the absolute risk of death among hospitalized children had a wide range depending on the site, time period and study methodology used. However, when the relative risk of death of HIV-infected children was compared to HIV-uninfected children, HIV-infected children had consistently higher case fatality across all the studies. There was no evidence that HIV infection in African children has less impact on measles severity than was observed in the USA in the late 1980's and early 1990's. There is good immunological reason to suppose that ART would decrease measles-specific CFR. However, as this has only been reported in 1 small retrospective cohort, there is not yet strong statistical evidence of the impact of ART on this specific aspect of overall child survival. There is need for ongoing measles surveillance in Africa, and vigilance from paediatric ART researchers to identify further risk factors for measles mortality among HIV-infected children in Africa.

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**Tables and figures**

Fig 1: Selection of eligible articles

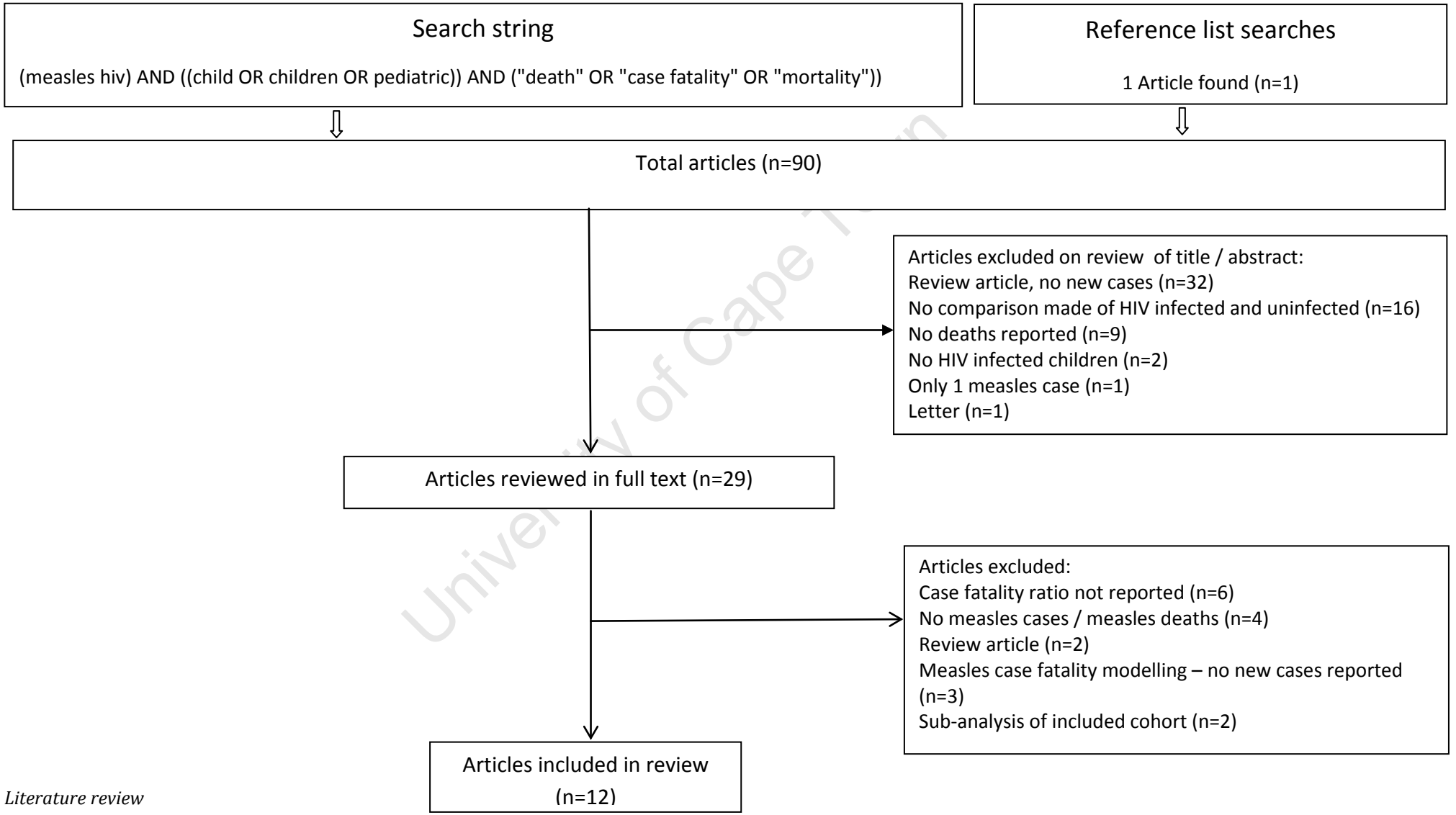

**Table 1.Description of case series of HIV-infected children**

| Study | Study design | Country; time period | Total no. HIV-infected patients reported | No. excluded (Reasons for exclusion) | No. new cases for analysis | Case fatality: HIV infected |
|---|---|---|---|---|---|---|
| MMWR 1988 | Case series of HIV-infected children with measles | USA, 1986-87 | 6 | 4 (subsequently included in Krasinski) | 2 | 1 / 2 (50%) |
| Krasinski, 1989 | Case series of HIV-infected children with measles | USA; time period not stated | 5 | 1 ( A young child < 9 months with indeterminate HIV status subsequently confirmed uninfected) | 4 | 1 / 4 (25%) |
| Palumbo, 1992 | Case series of HIV-infected children with measles | USA, 1990-1991 | 6 | (None excluded) | 6 | 3/6 (50%) |
| Kaplan, 1992 | Literature review of case reports and case series of HIV-infected children with measles | USA; time period not stated | 27 | 24 (1 was over 18 years old; 16 were included in Sension (1989); 5 included in Krasinski (1989); 2 included in MMWR) | 3 | 1/3 (33%) |
| Moss, 1999 | Literature review of case reports and case series of HIV-infected children with measles | USA; time period not stated | 19 | 15 (6 included in Palumbo; 5 included in Krasinski (1989); 2 included in MMWR, 2 included in Kaplan) | 4 | 0/4 |
| | | | | | Overall: 19 | 6/19 (33%) |

MMWR: Mortality and Morbidity Weekly Report



*Literature review*

**Table 2. Hospital / community cohorts of HIV-infected and uninfected children**

| Retrospective reviews | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Study design** | **Country; time period** | **Characteristics of study patients** | **Measles cases: Total** | **Measles cases: HIV-infected** | **Measles cases: Unknown HIV status** | **Measles deaths: Total** | **Case fatality: known uninfected** | **Case fatality: Indeterminate status** | **Case fatality: HIV infected** | **Relative risk: known HIV infected vs known HIV uninfected** |
| Jeena, 1998 | Retrospective chart review | South Africa; 1985-1996 | All children admitted to paediatric isolation / infectious disease units at Clairwood or King Edward VIII Hospitals | 11 077 | 10 | 10 979 / 11 077 (99.1%) | 861 | Data not presented | Data not presented | 5/10 (50%) | Data not presented |
| le Roux, 2012 | Retro-spective review | South Africa; Nov 2009 – July 2010 | All children identified with measles at a teaching hospital in Cape Town. | 1861 (Outpatients : 1309 Admissions: 552) | Admissions: 39 / 404 with known HIV status (10%) | Admissions: 148/552 (27%) | 18/552 (3%) | 11/365 (3.0%) | 0/148 | 7/39 (18%) | 4.69 (2.41 – 9.14)<br><br>Adjusted odds ratio: 7.55 (2.27 – 25.12) |
| McMorrow, 2009 | Retro-spective case tracing | South Africa; May-June 2005 | All children + adults with confirmed measles traced; patient / family interviewed | 109/349 cases traced and interviewed | <5 years: 14<br>>5 year: 9<br>unknown: 5 | 49 | Not reported | 2/46 (4.3%) | Not reported | 2/14 (14%) | 3.3 (0.51 – 21.2) |

| Prospective studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Study design** | **Country; time period** | **Characteristics of study patients** | **Measles cases: Total** | **Measles cases: HIV-infected** | **Measles cases: Unknown HIV status** | **Measles deaths: Total** | **Case fatality: known uninfected** | **Case fatality: Indeterminate status** | **Case fatality: HIV infected** | **Relative risk: known HIV infected vs known HIV uninfected** |
| Oshitani, 1996 | Prospective study of measles admissions | Zambia; Jan 1993 – June 1995 | Children 9-59 months with measles admitted to a teaching hospital in Lusaka | 356 | 36 seropositive >18 months | 32 seropositive <18 months | 43 / 356 (12%) | 24/288 (8.4%) | 9/32 (28%) | 10/36 (28%) | 3.28 (1.74 – 6.20) |
| Moss, 2008 | Prospective study of measles admissions | Zambia; Jan 1998 – July 2003 | All children with measles admitted to a teaching hospital in Lusaka | 1227 with known measles / HIV status | 189 / 1227 (7.2%) | 0 | 68 | 45/1038 (4.3%) | | 23/189 (12.2%) | 2.81 (1.74 – 4.53)<br><br>Adjusted odds ratio:2.5 (1.4 – 4.6) |
| Sension, 1988 | Prospective study of measles admissions | Zaire; Jan-March 1987 | Children <5 admitted to 2 hospitals in Kinshasa | 314 | 7 seropositive > 15 months | 9 seropositive <15 months | 87 / 308 (28%) patients with known outcome | 82/292 (28%) | 1/9 (11%) | 4/7 (57%) | 2.03 (1.04 – 3.96) |
| Birth cohort | | | | | | | | | | | |
| Embree, 1992 | Longitudinal birth cohort | Kenya; starting in 1986 | Infants born in a perinatal HIV transmission study, followed from birth for 3 years | 26 | 2 | 5 | 2 | 1 / 14<br><br>(7.1%) | 1 / 5<br><br>(20%) | 0/2 | |

Appendix 1 :

UCT Faculty of Health Sciences: Human Research Ethics Committee

# Form FHS013: New protocol application form – section A

## 1. General information

| | |
|---|---|
| Protocol title | Impact of measles epidemic at Red Cross Children's Hospital, 2009-2010: a retrospective record review |

## 2. Investigator(s) profile

| UCT's principal investigator (PI) | | | | |
|---|---|---|---|---|
| Title, first name, surname | Dr David le Roux | | | |
| Department/Division | Paediatric infectious disease unit | | | |
| Phone | 082 372 8449 | | | |
| Email address | David.leRoux@uct.ac.za | | | |
| Office mailing address | 4th Floor Laboratory, ICH building, Red Cross Children's Hospital | | | |
| Registration with HPCSA | √☐Yes | ☐ No | Registration # | MP 0506362 |

**Note:**

- If a non-medically trained PI is overseeing research which involves medical procedures, the application must include a medical doctor registered with the HPCSA as a co-investigator.
- The research must have a UCT-based principal investigator, co-investigator or supervisor.

**2.2 Co-investigator(s)**

| Title, first name, surname | Department/Division | E-mail |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

**2.3 How many of the following does the PI currently oversee?**

(Total number for all research projects)

| | | | |
|---|---|---|---|
| Open research studies | 0 | Sites (excluding this application) | 0 |
| Co-investigators | 0 | Number of participants | 0 |

| 2.4 What is the PI's role in authoring this protocol? (tick √) | |
|---|---|
| Primary author | √ |
| Collaborator | |
| None (developed by sponsors) | |

| 2.5 Are there any publication restrictions on the research? | |
|---|---|
| √☐ No | ☐ Yes |
| If yes, please describe and justify: | |
| | |

## 3. Protocol profile

| 3.1 Has this protocol been submitted to another Human Research Ethics Committee? (tick √) | | |
|---|---|---|
| √☐ No | ☐ Yes | |
| If yes, please complete: | Name of Institution | Outcome |
| | | |
| | | |
| | | |
| | | |

| 3.2 To your knowledge, has this protocol been rejected by another HREC? (tick √) | | |
|---|---|---|
| √☐ No | ☐ Don't know | ☐ Yes |
| If yes, please provide the reasons: | | |
| | | |

| 3.3 Is this application similar or related to research previously approved by this Committee? (e.g. a sub-study, follow-up study, earlier phase trial)? (tick √) | | |
|---|---|---|
| √☐ No | ☐ Yes | |
| If yes, please complete: | REC REF no. | Project title |
| | | |
| | | |

| **3.4 Is this protocol for degree purposes? (tick √)** | |
|---|---|
| ☐ No | ☐ √ Yes |
| If yes, please specify: | |
| Type of degree | M Phil (Paediatric infectious disease) |
| Student's name and e-mail | Dr David le Roux David.leRoux@uct.ac.za |
| Supervisor's name and e-mail | Prof Brian Eley<br>Brian.Eley@uct.ac.za |
| Department and University | School of Child and Adolescent Heath, UCT |

| **3.5 Does this protocol comply with the Helsinki Declaration of 2008? (tick √)** | |
|---|---|
| ☐ No | √☐ Yes |
| If no, please explain with full justification | |
| | |

| **3.6 Does the protocol provide insurance for research-related adverse events (tick √)** | | |
|---|---|---|
| ☐√ NA (e.g. minimal risk research, medical record review) | ☐ No | ☐ Yes |
| If yes, please describe: | | |
| ABPI-compliant corporate insurance policy | | |
| UCT's no-fault insurance policy | | |
| Other. Please specify | | |
| | | |

| **3.7 Does the protocol comply with UCT's intellectual property rights policy? (tick √)** | |
|---|---|
| ☐ √ Yes | ☐ No |
| If no, please justify | |
| | |

## 4. Funding and grant information

| **4.1 Funding source (tick √ at least one)** | |
|---|---|
| No funding/sponsor → skip to Q. 5 | √ |
| Agency-funded (e.g. MRC, NRF, Wellcome Trust, Bill and Melinda Gates Foundation) | |
| US Federal funding (e.g. NIH, CDC) | |
| UCT (e.g. departmental funding) | |
| Other. Please specify: | |

| 4.2 Ethics review levy (Industry-sponsored research only) | |
|---|---|
| For invoicing purposes, please provide: | |
| Sponsor's name | |
| Contact person | |
| Address | |
| Telephone number | |

**Note:** the HREC does not have the authority to waiver the ethics review levy. If a waiver is required, please contact Mr Salie Nassiep, the Research Management Accountant in the Faculty of Health Sciences (021 406 6409).

| 4.3 What is the total sponsorship/funding for this protocol? | |
|---|---|

| 4.4 Into what entity will the funding be paid? | |
|---|---|

| 4.5 Where applicable, has the PI negotiated an agreement with the hospital or other health or laboratory services to cover the costs of interventions/ procedures/ investigations performed solely for research purposes? (e.g. extra MRIs, CT scans, diagnostic tests, prolonged hospitalisation, use of non-research staff to collect research-related data or perform research-related procedures) (tick √) | | |
|---|---|---|
| ☐ NA | ☐ Yes | ☐ No |
| If no, please explain how research costs will be recovered | | |
| | | |

**Note:** a summary budget must be attached in the appendices.

## 5. Characteristics of the protocol

| 5.1 Category of research<br>Please select an appropriate category for your protocol. If the protocol falls in more than one category, please designate a primary and secondary category by entering a '1' and a '2'. | |
|---|---|
| Medical intervention/ clinical trial (e.g. drugs, devices, innovations) | |
| Behavioural/ psychosocial interventions (e.g. comparison of counselling programmes) | |
| Epidemiology/ observational study (e.g. survey, prevalence, case control, cohort studies) | |
| Quality improvement | |
| Testing new technologies | |
| Medical record review, audit | √ |
| Establishment of a specimen repository, medical data base/ registry | |
| Clinical laboratory studies | |
| Qualitative research (e.g. focus groups, in-depth interviewing, ethnography) | |
| Pilot study | |
| Other. Please describe: | |

| | | |
|---|---|---|
| **5.2 Category of participants** | ☐ Adults | ☐√ Minors (<18 years). Please specify age range: 0-16 yr |

| | |
|---|---|
| **5.3 Estimated number of participants** | About 1000 records |

| | |
|---|---|
| **5.4 Estimated duration of the study** | 9 months |

| **5.5 Location(s) of the study:** |
|---|
| Red Cross Children's Hospital |

| **5.6 Will non-English speaking participants be enrolled in the study? (tick √)** | | |
|---|---|---|
| ☐ √ NA | ☐ No | ☐ Yes |

If yes, please tick √ what measures will be used to promote participants' and families' understanding:

| | |
|---|---|
| Written translation of consent/ assent forms into Afrikaans | |
| Written translation of consent/ assent forms into Xhosa | |
| Use of trained translator(s)/ interpreter(s) | |
| Other. Please specify below and describe how the investigators intend to explain the study to potential | |
| | |

| **5.7 What measures will be taken to protect confidentiality (tick √)** | |
|---|---|
| Paper-based records will be kept in a secure location and only accessible to personnel involved in the study | √ |
| Computer-based records will only be available to personnel involved in the study through the use of access privileges and passwords | √ |
| Personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information | √ |
| Personal identifiers will be removed from research-related information | √ |
| Encryption | NA |
| Audio and/ or video recordings will be transcribed and then destroyed to eliminate identification of participants | NA |
| Use of pseudonyms | NA |
| Participants in focus groups will be advised that confidentiality cannot be assured | NA |
| Other. Please specify: | |

## 6. Clinical trials

| This section must be completed only if the research involves a clinical trial of drugs/ medicines, herbal, complementary or indigenous therapies; therapeutic devices; an innovative therapy or intervention; off-label use or a departure from standard treatment or care.<br>The SA GCP Guidelines (2006) define a clinical trial as any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the objective of ascertaining its safety and/or efficacy. | | |
|---|---|---|
| Is this protocol a clinical trial (tick √): | ☐ Yes | ☐ √ No (If no, please go to Q.7) |

| **6.1 Is the product registered with the Medicines Control Council (MCC)?** (tick √) | ☐ Yes | ☐ No |
|---|---|---|
| If yes, please provide the registration number | | |
| If no, is the MCC's letter for use of an unregistered medicine attached? | ☐ Yes<br>☐ No<br>☐ Application submitted | |

| If registered, will the product be studied for an **indication** different to that approved in the SA package insert? | ☐ Yes | ☐ No |
|---|---|---|
| If registered, will the product be studied using a **dose** different to that approved in the SA package insert? | ☐ Yes | ☐ No |
| If registered, will the product be studied using a **formulation** different to that approved in the SA package insert? | ☐ Yes | ☐ No |
| If registered, will the product be studied using **a route of administration** different to that approved in the SA package insert? | ☐ Yes | ☐ No |

**Note:** If yes to any of the above, MCC approval is required.

| **6.2 Does the study involve an FDA-monitored product (drug, device or biological)?** (tick √) | ☐ Yes | ☐ No |
|---|---|---|

| **6.3 Is this trial registered with the South African Clinical Trial Register?** | ☐ Yes | ☐ No |
|---|---|---|
| If yes, please provide the registration number | | |
| If no | ☐ Application submitted | |

| **6.4 Does this trial comply with the Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, 2nd Edition, 2006?** (tick √): | ☐ Yes | ☐ No |
|---|---|---|
| If no, please justify | | |

| | | |
|---|---|---|
| **6.5 Is the PI covered by professional liability insurance?** (tick √): | ☐ Yes | ☐ No |
| If yes, please provide Medical Protection number | | |

| **6.6 Trial design** (tick √ all that apply) | |
|---|---|
| ☐ Placebo-control | Please justify use of a placebo: |
| ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV<br>☐ Single centre ☐ National multi-centre ☐ International multi-centre<br>☐ Open label/ roll-over/ extension study. (If yes, a summary of the main findings, including safety and efficacy data, from the previous study must be included in the appendices. This is a requirement for HREC review.) | |

| | | |
|---|---|---|
| **6.7 Is the PI free to publish the findings of this trial?** (tick √) | ☐ Yes | ☐ No |
| **If no**, please describe the conditions of publication. | | |

## 7. Statement of conflict of interest

| The PI is expected to declare any existing or potential conflict of interest that may affect the scientific integrity and ethical conduct of this research. For purposes of this section, 'immediate family' means the PI's spouse or domestic partner and dependent children. Please tick √ all that apply: | |
|---|---|
| I, or any member of my immediate family, do not have any interest related to this research (e.g. financial interest in the sponsor of the research or intervention being tested.) | √ |
| I, or any member of my immediate family, do not have a proprietary interest in the product being tested in this research (e.g. patent, trademark, copyright, licensing agreement). | |
| I, or any member of my immediate family, do not have any relationships related to this research (e.g. board membership, consultative, executive, employment) or any entity with an ownership interest in the research other than the relationship of sponsor-investigator. | |
| As Principal Investigator of this research I am aware of a potential conflict of interest. Please describe and provide a plan to manage the conflict of interest in the space below: | |
| | |

## 8. Declarations and Signatures

| This application will not be processed unless all the required declarations and signatures are completed according to the Committee's Standard Operating Procedures. | | | |
|---|---|---|---|
| **8.1 Head of Department or Division**<br>My signature confirms that:<br>i. The researcher(s)/student(s)/supervisor(s) have the skills, training, experience and time to undertake this research.<br>ii. There are adequate resources (e.g. equipment, space, support services) to perform this research. | | | |
| Signature of Head | | Date | |
| Print name | | | |

**Note:** Where the PI is also Head of Department, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

| **8.2 Chairperson of the Departmental Research Committee (DRC)**<br>My signature confirms that:<br>i. This research has undergone peer review by a person(s) experienced in the field of study.<br>ii. This research is well-designed and scientifically sound.<br>iii. Where relevant, all methodological issues have been resolved to the satisfaction of the peer reviewer(s).<br>iv. If conducted according to the protocol, this research is expected to yield valid and useful findings. | | | |
|---|---|---|---|
| Signature of Chairperson | | Date: | |
| Print name | | | |

**Note:** Where the PI is also the Chairperson of the DRC, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

| **8.3 Student supervisor (if research is for a degree)**<br>My signature confirms that:<br>i. The student researcher has adequate training and resources to complete the research in the allocated timeframe.<br>ii. The research has scholarly merit.<br>iii. The level of risk inherent in the study is commensurate with the student researcher's experience and the extent of oversight that I will provide.<br>iv. I will meet the student on a regular basis to monitor progress and address any problems that may arise during the study.<br>v. If applicable, I will ensure that the research undergoes continuing review as required by the HREC.<br>vi. If applicable, I will ensure that the student researcher reports unanticipated problems or serious adverse events to the HREC.<br>vii. I will arrange for an alternative faculty supervisor to take responsibility for this research during periods of absence such as sabbatical or annual leave. | | | |
|---|---|---|---|
| Signature of Supervisor | | Date: | |
| Print name | Prof Brian Eley | | |

**Note:** The supervisor and student researcher are jointly responsible for the ethical conduct of this research from inception to dissemination of findings.

**8.4 Principal investigator**
My signature confirms that:

i. Information in this application is true and accurate.
ii. I will begin the research only after HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iv. I will conduct the research according to all ethical, regulatory and legal requirements laid down in the HREC's Standard Operating Procedures.
v. I will provide progress reports to the HREC as requested, including a final closing report at the end of the research.
vi. I will notify the HREC in writing if any change to the research is proposed and await approval before proceeding with the proposed change except when urgently necessary to protect participants' safety.
vii. I will notify the HREC in writing immediately if any adverse event or unanticipated problem occurs during the research.
viii. I will allow an audit of my research if requested by the HREC.
ix. I have the time, training, experience and resources to oversee this research.

| | | | |
|---|---|---|---|
| Signature of PI | | Date: | 12/10/2010 |
| Print name | David le Roux | | |

## New protocol submission checklist

Please ensure that all the applicable sections are fully completed and included in the submission. Missing information will delay the review process as the application will be returned to the PI. Sections A-C must be included. Instructions for submission of new applications are posted on the HREC website.

Have you included?

- ☐ Section A: New Protocol Application Form
- ☐ Section B: Synopsis
- ☐ Section C: Research Protocol
- ☐ Appendices (as applicable):
  - ☐ Sponsor's protocol
  - ☐ NIH or other US federal grant application (if PI is primary awardee)
  - ☐ Investigator's brochure and package inserts
  - ☐ Surveys, questionnaires, interview schedules
  - ☐ Recruitment materials: advertisements, flyers, posters
  - ☐ Materials for participants: diaries, patient identification cards, newsletters, educational pamphlets
  - ☐ Consent and assent forms (English versions)
  - ☐ Letters of authorisation from institutions such as hospitals, clinics and schools
  - ☐ A summary of Phase III efficacy and safety data if this is an application for an open label or extension of a previously approved study
  - ☐ Budget summary
  - ☐ MCC letter of approval, if available
  - ☐ If an application has been submitted to the MCC, a copy of Section 13 (Ethical Issues) extracted from the CTF1 application form
  - ☐ In the case of clinical trials, PI's declaration, CVs and GCP certificates for PI and co-investigators
- ☐ Other relevant documentation

| | |
|---|---|
| Please submit the completed protocol together with an electronic copy to: | **Mrs Lamees Emjedi**<br><br>Research Ethics Committee<br>E 52 Room 24, Old Main Building, Groote Schuur Hospital, Observatory<br>Telephone: 27 21 406 6338<br>Fax: 27 21 406 6411<br>Email: Nosi.Tywabi@uct.ac.za |

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
**Telephone** [021] 406 6626 • **Facsimile** [021] 406 6411
**e-mail:** lamees.emjedi@uct.ac.za

**10 November 2010**

**HREC REF: 511/2010**

**Dr D Le Roux**
Paediatric Infectious Diseases Unit
Paediatric
Red Cross

Dear Dr Le Roux

**PROJECT TITLE: IMPACT OF MEASLES EPIDEMIC AT RED CROSS CHILDREN'S HOSPITAL, 2009-2010: A RETROSPECTIVE RECORD REVIEW**

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 FHS HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until 15 November 2011.**

Please send us an annual progress report (website form FHS 016) if your research continues beyond the approval period. Alternatively, please send us a brief summary of your findings so that we can close the research file.

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

**Please quote the REC. REF in all your correspondence.**

Yours sincerely

Wesley Kinsley

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, HSF HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

lemjedi

UNIVERSITY OF CAPE TOWN
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**FACULTY OF HEALTH SCIENCES**
Human Research Ethics Committee

# FHS017: Annual progress and study closure report

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

## 1. Protocol information

| | |
|---|---|
| Date | 30 December 2011 |
| HREC REF Number | HREC REF 511/2010 |
| Protocol number (if applicable) & Protocol title | Impact of measles epidemic at Red Cross Children's Hospital, 2009-2010: a retrospective record review |
| Principal Investigator | David le Roux |
| Department / Office Internal Mail Address | Dept Paediatrics and Child Health, Red Cross Children's Hospital<br>David.leRoux@uct.ac.za |

RESEARCH ETHICS COMMITTEE
2012 -01- 06
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

| | | |
|---|---|---|
| 1.1 Does this protocol receive US Federal funding? | ☐ Yes | ☑ No |

## 2. Protocol status (tick ✓)

| | |
|---|---|
| ☐ | Research-related activities are ongoing |
| ☑ | Data collection is complete, data analysis only |
| ☐ | All research-related activities are complete (i.e. final report) |

## 3. Protocol summary

| | |
|---|---|
| Total number of records or specimens collected, reviewed or stored since the original approval | 1859 |
| Total number of records or specimens collected, reviewed or stored since last progress | N/A |
| Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research?<br>If yes, please list and attach with this report. | ☑ Yes<br>Poster presented at FIDSSA conference, Durban, September 2011 |

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.

| | | | |
|---|---|---|---|
| Signature of PI | | Date | 30/12/2011 |
| Signature of Supervisor (if PI is a student) | | Date | 30/12/2011 |

| HREC office use only (FWA00001637; IRB00001938) | | | |
|---|---|---|---|
| This serves as notification of annual or final approval, including any documentation described above. | | | |
| ☑ Approved | Annual progress report | | |
| OR ☐ Approved | Study closure report | | |
| ☐ Not approved | See attached comments | | |
| Expiry date | 15 JANUARY 2013 | | |
| Signature<br>Chairperson of the HREC | | Date | 9/1/2012 |

RESEARCH ETHICS COMMITTEE

2012 -01- 06

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

# Appendix 2:

# South African Medical Journal submission

# Author Guidelines

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Material submitted for publication in the South African Medical Journal (SAMJ) is accepted provided it has not been published elsewhere. The SAMJ reserves copyright of the material published.

The SAMJ does not hold itself responsible for statements made by the authors.

**AUTHORSHIP**

All named authors must give consent to publication. Authorship should be based only on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; (iii) final approval of the version to be published. All three of these conditions must be met (Uniform requirements for manuscripts submitted to biomedical journals; www.icmje.org/index.html).

**RESEARCH ETHICS COMMITTEE APPROVAL**

**Evidence must be provided of Research Ethics Committee approval of the research where relevant.**

**CONFLICT OF INTEREST**

**Authors must declare all sources of support for the research and any association with the product or subject that may constitute conflict of interest.**

**PROTECTION OF PATIENT'S RIGHTS TO PRIVACY**

**Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. Informed consent for this purpose requires that the patient be shown the manuscript to be published. (www.icmje.org)**

**ETHNIC CLASSIFICATION**

**Work that is based on or contains reference to ethnic classification must indicate the rationale for this.**

**MANUSCRIPTS**

**Short items are more likely to appeal to our readers and therefore to be accepted for publication.**

***Original articles* of 3 000 words or less, with up to 6 tables or illustrations, should normally report observations or research of relevance to clinical medicine. References should preferably be limited to no more than 15.**

***Short reports or scientific letters*, which include case reports (the SAMJ is rarely able to publish case reports), side effects of drugs and brief or negative research findings should**

**be 1000 words or less, with 1 table or illustration and no more than 6 references.**

***Editorials, Opinions, Issues in Medicine*, etc. should be about 800 words and are welcome, but unless invited, will be subjected to the SAMJ peer review process.**

***Review articles* are rarely accepted unless invited.**

***Letters to the editor*, if intended for the correspondence column should be no longer than 400 words with only one illustration or table.**

***Obituaries* should not exceed 400 words and may be accompanied by a photograph.**

**MANUSCRIPT PREPARATION**

**Research articles should have a structured abstract not exceeding 250 words (50 for short reports) comprising: Objectives, Design, Setting, Subjects, Outcome measures, Results and Conclusions.**

**Refer to articles in recent issues for guidance on the presentation of headings and subheadings.**

**Abbreviations should be spelt out when first used in the text and thereafter used consistently.**

**Scientific measurements should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl.**

**If in doubt, refer to 'uniform requirements' above.**

**ILLUSTRATIONS**

**Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain written consent to republication from the copyright holder and the author(s). All illustrations, figures etc. must be of high resolution/quality, preferably jpeg or equivalent but not powerpoint, and preferably attached as supplementary files.**

**REFERENCES**

**References should be inserted in the text as superior numbers and should be listed at the end of the article in numerical and not in alphabetical order.**

**Authors are responsible for verification of references from the original sources.**

**References should be set out in the Vancouver style and approved abbreviations of journal titles used; consult the List of Journals in Index Medicus for these details.**

**Names and initials of all authors should be given unless there are more than six, in which case the first three names should be given followed by et al. First and last page numbers should be given.**

**Journal references should appear thus:**

**Price NC . Importance of asking about glaucoma. BMJ 1983; 286: 349-350.**
**Book references should be set out as follows:**

**Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975: 96-101.**
**Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974: 457-472.**
**Manuscripts accepted but not yet published can be included as references followed by (in press).**

**Unpublished observations and personal communications may be cited in the text, but not in the reference list**

**PROOFS**
**Proofs will be forwarded to the author before publication and if not returned within 2 weeks will be regarded as approved. Alterations at this stage are costly and may be charged to the authors.**

**CHANGES OF ADDRESS**
**Please notify the Editorial Department of any address changes so that proofs etc. may be sent without delay.**

**CPD POINTS**
**Authors can earn up to 15 CPD points for published articles. Certificates may be requested after publication of the article.**



# Submission Preparation Checklist

**As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.**

1. **The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).**
2. **The submission file is in Microsoft Word or RTF document file format.**
3. **When available, the URLs to access references online are provided, including those for open access versions of the reference. The URLs are ready to click (e.g., http://pkp.sfu.ca).**
4. **The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses). Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain**

written consent to republication from the copyright holder and the author(s). All illustrations, figures etc. must be of high resolution/quality, preferably jpeg or equivalent but not powerpoint, and preferably attached as supplementary files.

5. The text adheres to the stylistic and bibliographic requirements in Author Guidelines, which is found in About the Journal.
6. Research Ethics Committee approval was obtained for the research (this should be indicated in the text of the paper).
7. Authors must indicate any conflict of interest (or competing interests).

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ISSN:2078-5135

PO Box 159
Newlands
7725, Cape Town
South Africa
1 June 2012

The Editor
South African Medical Journal

Dear Prof van Niekerk

**Re: Submission of revised manuscript**

Attached please find the revised manuscript "South African measles outbreak 2009-2010: experience of a paediatric hospital".

Revisions have been made as suggested. The manuscript is shorter and contains fewer references. There have been several minor grammatical changes; figures and tables remain unchanged. Substantial revisions to content are listed below:

Page 3: Study population: formula to calculate length of stay removed
Page 4: HIV testing: reference to rapid testing omitted
Page 6: Admissions: Sentence comparing baseline characteristics of children with unknown HIV status to children with known HIV status omitted.
Page 6: Deaths and complications: paragraph re nosocomial measles omitted
Page 7: Length of stay and complications: details of 2nd and 3rd admissions (length of stay median and IQR) omitted
Page 8: Discussion paragraph 2: Reference to French vaccination study omitted
Page 8: Discussion paragraph 4: Case fatality paragraph shortened, and references to nosocomial measles omitted
Page 9: Discussion paragraph 6: Comment on re-admission of HIV infected children with measles
Page 10: Discussion paragraph 8: Reference to "Dermatological manifestations of measles" (SAMJ June 2012)

I trust all will be in order.

Regards
Dr David le Roux
MBCHB, FCPaed, MPH

DrDaveleRoux@gmail.com

# South African measles outbreak 2009 - 2010 as experienced by a paediatric hospital

**David M le Roux, Stanzi M le Roux, James J Nuttall, Brian S Eley**

*Introduction.* Between 2009 and 2010, South Africa experienced a major measles outbreak, with more than 18 000 confirmed cases reported to the National Institute of Communicable Diseases.

*Methods.* We studied measles admissions during the outbreak to Red Cross War Memorial Children's Hospital, Cape Town, between 1 November 2009 and 31 July 2010. Factors associated with mortality were retrospectively identified from notification records and hospital admissions data. Multivariate logistic regression was used to investigate potential risk factors for death.

*Results.* In total, 1 861 children were diagnosed with measles; 552 (30%) were admitted to hospital. The most common reason for admission was pneumonia (379 (68%)) and/or diarrhoea (262 (48%)). The median age at admission was 7.36 months (interquartile range (IQR) 5.0 - 10.7). The median duration of admission was 4 days (IQR 2 - 6); total hospital admission time was 3 746 days (10.3 child-years). HIV status was known in 404 (73%) children: 39/400 (14%) were HIV-infected. Eighteen children died (3% of all admissions); 15 (83%) of them were less than 1 year old. In the regression model, HIV-infection (adjusted odds ratio (aOR) 7.55, 95% confidence interval (CI) 2.27 - 25.12) and female sex (aOR 3.86, 95% CI 1.26 - 11.84) were associated with higher odds of death.

*Conclusions.* There was a large paediatric admission burden during the 2009 - 2010 measles outbreak in Cape Town; young children were predominantly affected. HIV-infected children had a significantly higher case fatality.

*S Afr Med J* 2012;102(9):760-764. DOI:10.7196/SAMJ.5984

*Infectious Diseases Unit, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and University of Cape Town*
**David M le Roux,** MB ChB, DTM&H, FCPaed (SA), MMed (Paed), MPH
**James J Nuttall**, MB ChB, FCPaed (SA), DTM&H
**Brian S Eley,** MB ChB, BSc, FCPaed (SA)

*Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and University of Cape Town*
**Stanzi M le Roux,** MB ChB, DCH

***Corresponding author:*** *D le Roux (DrDaveleRoux@gmail.com)*

Measles vaccination has been very effective in reducing the global measles disease burden. However, outbreaks can occur when inadequate vaccination coverage allows accumulation of a sufficient number of susceptible individuals in a population. The estimated level of population immunity needed to prevent measles outbreaks is about 95%.[1] South Africa introduced routine measles vaccination in 1975, and measles became a notifiable condition in 1979. In 1995, the current 2-dose strategy (routine vaccination at 9 and 18 months) was adopted. Case-based surveillance was introduced in 1998, with all suspected cases having blood or urine tested at the National Institute of Communicable Diseases (NICD).[2]

Accurate coverage of measles vaccination has been difficult to determine. In 2009, the South African Department of Health (DoH)

estimated national coverage with routine measles vaccine to be 99%, but the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) coverage estimates were only 65%.[3] In 2004, a survey in Western Cape Province found 79% of children to be 'fully vaccinated'.[4] In 2005, another study estimated that 93% of children had received the first dose of measles vaccine, but only 60% a second dose.[5] The authors concluded that routine coverage in the Western Cape was too low to prevent a measles outbreak.

The last major outbreak in South Africa occurred in 1992. In July 2009, a cluster of measles cases was detected in Tshwane; in August, the outbreak spread to Johannesburg, and then rapidly throughout the rest of the country. The first case in the Western Cape was confirmed in September 2009; there were 14 cases in October, and by November the outbreak was well established throughout the Cape Town metropole.[6] We report the epidemiology of measles cases presenting to a single paediatric hospital in Cape Town.

## Methods

Red Cross War Memorial Children's Hospital (RXH) is a 290-bed, level 3 academic hospital in Cape Town. During the outbreak, children with measles who needed admission were stabilised and admitted to the 'short stay ward', from which they were either discharged home, transferred to another hospital (mild disease), or admitted to the medical wards or Intensive Care Unit (ICU) at RXH (severe disease or other significant co-morbid disease).

All children diagnosed with measles at RXH between 1 November 2009 and 31 July 2010 were retrospectively identified from paper notification records, electronic hospital admission records, and the ICU database. Folders were reviewed and patients meeting the WHO clinical case definition were included.[7] Suspected measles cases that tested negative for measles IgM antibodies were excluded. Data were captured onto a paper form and entered into an electronic database. Final discharge dates and re-admission dates were extracted from the city-wide hospital admission computer system; this includeD all the time spent in any hospital in the city.

All children were managed according to written hospital protocols. In-patient management of pneumonia included intravenous ampicillin, gentamicin and cloxacillin. Vitamin A was dosed according to WHO guidelines.[7] During the outbreak, all children attending RXH who did not have clinical measles were given measles prophylaxis. Children older than 6 months were given a single dose of intramuscular measles vaccine (Rouvax, Sanofi Pasteur, France); children under 6 months and children with severe immunosuppression were given an intramuscular dose of human immunoglobulin (Intragam, National Bioproducts Institute, South Africa), according to the manufacturer's instructions.

HIV testing was performed when deemed clinically appropriate by the treating clinicians. Children >18 months old were considered HIV-infected if HIV antibodies were detected by enzyme-linked immunosorbent assay (ELISA) testing. Results were confirmed on a second specimen with a manual ELISA (Enzygnost Anti-HIV 1/2 Plus, Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany). Children <18 months old were considered HIV-infected with positive HIV DNA PCR (Cobas Ampliprep system, Roche Molecular Systems, Branchburg, New Jersey, USA). Positive HIV DNA PCR results were confirmed with HIV viral load testing.

For summary statistics, categorical data are expressed as number (percentage); continuous data are expressed as median (inter-quartile range (IQR)). Median values were compared with the Wilcoxon rank-sum test. Risk ratios were calculated to compare the proportion of children who died or were re-admitted by gender and HIV status.

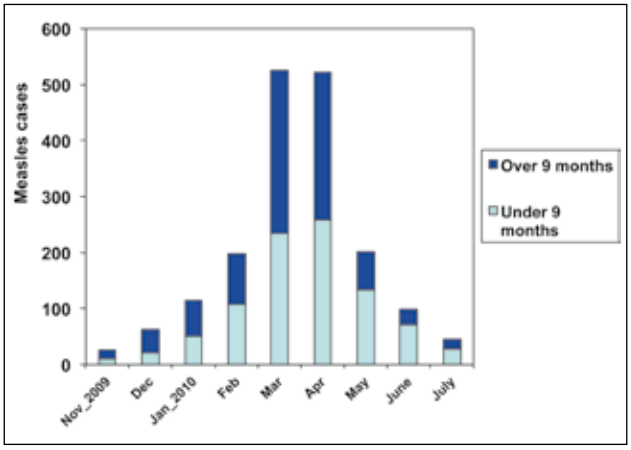


*Fig. 1. Measles cases by month.*

Factors associated with death were explored with multivariable logistic regression. We evaluated the influence of age, sex, HIV status, immunisation status, evidence of vitamin A administration, the presence of a 'Road to Health Card' and the weight-for-age Z-score (calculated from growth charts from the Centers for Disease Control and Prevention (CDC)). Weight-for-age Z-score of less than -2 was considered 'moderate underweight for age'; and less than -3 was considered 'severe underweight for age'. Variables associated with the outcome at the α=0.1 level were included for multivariable analysis. Automated backwards and forwards step-wise model building procedures were used; potential models were compared with Akaike's Information Criteria (AIC). Collinearity was assessed with variance inflation factors. The final model chosen was most parsimonious and presented the best AIC value. A sensitivity analysis was done to examine the influence of the children with unknown HIV status. Analyses were done in Stata version 10 (Statacorp, College Station, Texas, USA). All *p*-values are two-tailed (α=0.05).

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, HREC-REF number 511/2010.

## Results

From 1 November 2009 to 31 July 2010, 1 861 children with measles presented to RXH, who have been categorised as follows.

### Outpatients

In total, 1 309 (70%) children were treated as outpatients; most presented in March and April 2010 (Fig. 1). The median age was 8.9 months (IQR 6.1 - 30.4) (Table 1). Documentation of measles vaccination status in the hospital notes was poor: of the 565 children eligible for routine measles vaccination, only 270 (48%) had vaccination status recorded, and only 68% had vitamin A administration documented in the hospital notes (Table 1).

### Admissions

There were 552 hospital admissions; inpatients were significantly younger than children treated only as outpatients (median age 7.4 months v. 8.9 months, Wilcoxon $p<0.0001$) (Table 1). Most children (357/552 (65%)) were younger than 9 months (the age of routine measles vaccination) (Fig. 2). At least 379 (63%) children presented with pneumonia, 262 (47%) with severe diarrhoea and 163 (30%) with both. Other reasons for admission included croup (37 (7%)), and suspected meningitis (2 (0.4%)). Vaccination status was recorded in the hospital notes in 92/195 (47%) children older than 9 months;

**Table 1. Characteristics of children with measles treated as outpatients and admitted to hospital**

| | Outpatients *n*=1 309 | Inpatients *n*=552 | Total *N*=1 861 |
|---|---|---|---|
| Age: months: median (IQR) | 8.9 (6.1 - 30.4) | 7.36 (5.0 - 10.7) | 8.3 (5.7 - 21.9) |
| Eligible for routine vaccination (>9 months) | 565/1 309 (43%) | 195/552 (35%) | 760/1861 (41%) |
| Vaccination status documented in hospital notes | 270/565 (48%) | 92/195 (47%) | 362/760 (48%) |
| At least 1 dose of measles vaccine documented in hospital notes | 125/270 (46%) | 40/92 (45%) | 165/362 (46%) |
| Vitamin A: | | | |
| Given | 895 (68%) | 522(95%) | 1 447 (78%) |
| Not documented in hospital notes | 414 (32%) | 30 (5%) | 444 (22%) |
| Boys | 610 (47%) | | 902 (48%) |
| Girls | 526 (40%) | 292 (53%) | 786 (42%) |
| Unknown | 174 (12%) | 260 (47%) | 174 (9%) |
| HIV status | | | |
| Known HIV status | | 404/552 (73%) | |
| HIV uninfected | | 369/404 (90%) | |
| HIV infected | | 39/404 (10%) | |
| On ART | | 20/39 (51%) | |
| Weight-for-age Z-score (IQR) | | -0.76 (-1.73 - 0.24) | |
| Road to Health Card seen | | | |
| Yes | | 323 (58%) | |
| No | | 68 (12%) | |
| Not documented | | 161 (30%) | |
| Notified | | | |
| Yes | | 382 (69%) | |
| No | | 139 (25%) | |
| Not documented | | 31 (6%) | |
| Confirmed cases (IgM) | | 96/552 (17%) | |
| Median length of stay: days (IQR) | | 4 (2 - 6) | |
| Outcome: | | | |
| Died | | 18 (3%) | |
| Discharged home | | 354 (64%) | |
| Transferred out | | 179 (33%) | |
| Number readmitted (<30 days) | | 72/534 (13%) | |

IQR = inter-quartile range; ART = anti-retroviral therapy.

**Table 2. Deaths by sex, age, HIV status and vaccination status**

| | Total deaths/total children (%) |
|---|---|
| Age | |
| <9 months | 12/357 (3.4%) |
| >9 months | 6/195 (3.1%) |
| Sex | |
| Male | 5/292 (1.7%) |
| Female | 13/260 (5.0%) |
| HIV status | |
| HIV-infected | 7/39 (18.0%) |
| HIV uninfected | 11/365 (3.0%) |
| Unknown | 0/148 |
| Vaccination status | |
| Any measles vaccination | 1/93 (1.1%) |
| Never vaccinated | 11/215 (5.1%) |
| Unknown | 6/244 (2.5%) |
| Total | 18/552 (3.2%) |

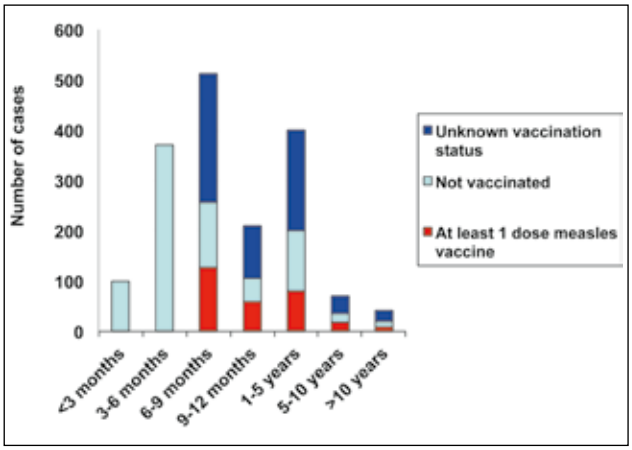


*Fig. 2. Number of measles cases by age and vaccine status.*

only 40/92 (45%) had had any measles vaccine documented in the hospital notes (Fig. 2). During the study period, venous blood for serological testing was sent from 102 children admitted with

**Table 3. Odds ratios (unadjusted and adjusted) of death**

| | Unadjusted OR (95% CI) | *p*-value | Adjusted OR (95% CI) | *p* value |
|---|---|---|---|---|
| Weight-for-age Z-score | 0.70 (0.56 - 0.88) | 0.002 | 0.65 (0.47 - 0.91) | 0.012 |
| Sex | | | | |
| Male | 1 | | 1 | |
| Female | 3.02 (1.06 - 8.59) | 0.038 | 3.86 (1.26 - 11.84) | 0.018 |
| HIV status | | | | |
| HIV uninfected | 1 | | 1 | |
| HIV infected | 7.04 (2.55 - 19.41) | <0.0001 | 7.55 (2.27 - 25.12) | 0.001 |

*Adjusted for age and weight-for-age Z-score.

suspected measles; 96 (17%) had detectable measles IgM antibodies; 4 specimens were invalid or insufficient. Only 2 children with clinically-suspected measles were confirmed measles IgM negative; both children had detectable rubella IgM antibodies, and were excluded from this analysis.

Of the admitted children, 404 (73%) had known HIV status: 39/404 (10%) were HIV-infected, of whom 20/39 (51%) had been on antiretroviral therapy (ART) for more than 3 months. All HIV-infected children with severe measles subsequently commenced ART. Only 3/23 (14%) HIV-infected, vaccine-eligible children had documentation of any measles vaccination.

### Deaths and complications

Of all admissions, 18 (3%) children died, of whom 13 (72%) were less than 1 year old; 11 (61%) deaths were due to respiratory failure; other causes included septic shock with multi-organ failure (4 children (22%)) and cerebral ischaemia after cardio-respiratory arrest (2 children (11%)). One child died from massive bowel ischaemia and necrosis.

Of HIV-infected children 7/39 (18%) died v. 11/365 (3%) known HIV-uninfected children. Case fatality was 5% among girls v. 1.7% of boys (Table 2). In multivariable logistic regression adjusted for age and weight-for-age, HIV infection and gender remained strong predictors of mortality (Table 3). Of HIV-infected children who died, 2/7 (29%) had received ART for at least 3 months.

During the study period, 4 children with complications of measles required tracheostomies (Sr Jane Booth, personal communication). One child was referred with severe croup; 3 children developed upper airway damage following prolonged intubation and ventilation for severe pneumonia. All 4 entered the RXH home tracheostomy programme and were discharged home within 2 months of their admission but had recurrent re-admissions with respiratory infections. By March 2012, 3 children had been successfully decannulated, and one remains with a tracheostomy.

### Length of stay and re-admissions

The median duration of admission was 4 days (IQR 2 - 6 days). HIV-infected children were admitted for longer (median 6 days, IQR 4 - 14 days) than HIV-uninfected children (median 3 days, IQR 2 - 5 days; Wilcoxon $p$=0.0007).

Among survivors, 53/287 (18%) of boys were re-admitted v. 19/247 (8%) of girls (risk ratio (RR) for re-admission 2.40 (95% CI 1.46 - 3.94, $p$=0.0003)). Moderate or severe underweight for age (weight for age Z-score less than -2) was also strongly associated with readmission: of 531 surviving children with known weight-for-age, 26/113 (23%) who were moderately or severely underweight for age were re-admitted v. 46/418 (11%) of children who were not underweight for age, RR 2.09 (95% CI 1.36 - 3.23, $p$=0.0009). Of HIV-infected children, 28% (9/32) were re-admitted v. 12% (44/354) HIV-uninfected children (RR 2.26, 95% CI 1.22 - 4.20, $p$=0.01).

Total primary hospital admission time was 3 746 days (10.3 child-years). Of the 534 surviving children, 72 (13%) were re-admitted within 90 days; 24 of these children (24/534 (4% of all the survivors)) were re-admitted a third time within 90 days of their first admission. The total time spent in hospital, including the primary admission and subsequent re-admissions within 3 months of discharge, was 4 477 days (12.3 child-years). This constitutes 6.6% of total in-patient days at RXH during the study period.

## Discussion

Between April 2009 and November 2010, South Africa experienced a national measles outbreak, with 18 311 serologically confirmed measles cases. Almost a quarter of these cases were infants younger than 9 months.[8] The magnitude was probably even greater, as many cases were diagnosed clinically: in our institution, only 96/552 (17%) measles admissions were laboratory confirmed.

At RXH, the main burden of disease, in terms of hospitalisations and mortality, was in infants <1 year old. There was an especially high burden in infants younger than 6 months. There are several reasons why the very young were so severely affected. Children become susceptible to measles infection once maternally-derived transplacental antibody levels are below a protective threshold. Vaccinated women transfer fewer antibodies than mothers whose immunity followed wild-type measles infection. In Belgium, babies of vaccinated women received a third of measles-specific antibodies v. babies born to women with immunity owing to natural measles infection.[9] The antibodies are also lost more quickly: the median time to loss of immunity was 0.97 months for babies born to vaccinated women v. 3.78 months for babies born to women with previous measles infection.[9]

In Cape Town, there has been little circulating measles virus since the 1992 outbreak; most women of childbearing age have not had natural measles infection. Since its inception in 1975, the coverage of the measles immunisation programme has been too low; many women have never been vaccinated. Their babies received no measles-specific antibodies, rendering them susceptible to measles infection from a very young age.

Case fatality of measles can range from 0.1% in developed countries to 30% in outbreaks among refugee populations. The incidence is influenced by age, intensity of exposure to measles virus, nutritional status, vaccination status, immune deficiency, vitamin A administration, and access to appropriate case management.[10] During the outbreak under review, case fatality among inpatients at RXH was 3% (18 deaths out of 552 admissions). Low weight-for-age Z-score was strongly associated with increased mortality, with 35% increased odds of death for every standard deviation below the expected weight for age. Furthermore, among survivors, low weight for age Z-score doubled the risk of re-admission. The finding of similar measles incidence among boys and girls, but with increased mortality among

girls, has previously been described,[11] but the biological mechanism is not well understood.

We observed increased case fatality among inpatients with HIV-infection. They had an 18% case fatality ratio, and 7 times higher odds of death than HIV-uninfected children, despite half of them being established on ART. This figure is higher than previously reported in areas with high HIV prevalence. In the 2003 - 2005 measles outbreak in Johannesburg, 14% of known HIV-infected children died; they had a 3.3 times higher risk of death than HIV-uninfected children.[12] In a 6-year study in Zambia, case fatality among HIV-infected children was 12%, with 2.5 times higher odds of death than HIV-uninfected children.[13] Our higher case fatality may reflect a selection bias for disease severity, as children admitted to RXH had more severe disease than children treated as outpatients or in other facilities in the city.

For several reasons, HIV-infected children have a more severe clinical course than HIV-uninfected children. HIV-infected children have deficient cellular and humoral immunity and impaired innate immune responses.[14] Despite commencing ART, HIV-infected children had twice the risk of re-admission v. HIV-uninfected children, which may reflect the combined immune-suppressive effect of acute measles infection in an already-compromised individual. HIV-infected children have suboptimal responses to measles vaccination. Vaccination, even if not fully protective against measles infection, can attenuate severity of disease.[10] In HIV-uninfected children, response to measles vaccination is age-dependent, with better antibody responses in older children. At 9 months, about 90% will develop protective antibody levels (interquartile range 82 - 95%); at 12 months, 99% will develop protective levels after a single dose of measles vaccine, (interquartile range 93 - 100%).[7] However, the response in HIV-infected children to vaccination does not improve with age. A meta-analysis of 26 studies of vaccine responses in HIV-infected children at different ages showed highly variable responses, but no trend towards improved seroconversion among older children. The efficacy of a single dose of measles vaccine, whether given at 6, 9 or 12 months, was about 59% (95% CI 46 - 71%).[15] These studies only reported attainment of protective antibody levels, and did not take into account T-cell mediated immunity, effectiveness of protection from clinical disease, or the effect of commencing ART. However, in a retrospective analysis of the 2003 - 2005 measles outbreak in Johannesburg, effectiveness of measles vaccine in preventing clinical disease among HIV-infected children was calculated at 63%.[12] Infants born to HIV-infected mothers who are themselves uninfected (HIV-exposed but uninfected) also have increased susceptibility to measles infection. HIV-exposed infants have lower levels of maternal antibody, and protective antibody is lost earlier than in HIV unexposed infants.[16]

Among the children admitted to hospital, there were 69 possible 'vaccine failures' – children with a record of at least 1 dose of measles vaccine, who developed severe clinical disease requiring admission. There are several possible explanations for these vaccine failures. When vaccinations were documented, the admitting clinician noted whether measles vaccine had been given, but not the date of administration. It was not possible to determine retrospectively the age at vaccination or time from vaccination till clinical disease. All children >6 months old received measles vaccine if they attended hospital, and there were 2 nationwide mass vaccination campaigns (12 - 23 April and 24 - 28 May 2010). However, vaccination of young children is less effective than of children >1 year old.[7] Some children might already have been infected with measles, but were vaccinated while in the incubation period. All children <6 months old seen at the hospital who did not have measles were given measles immune globulin. If these children were subsequently vaccinated, the immune globulin could impair vaccine effectiveness for up to 9 months.[17] If they developed clinical measles despite having had a vaccine dose recorded in their Road to Health Card, they would be considered vaccine failures.

This study has several limitations. The data were captured retrospectively from clinical case notes, much data had not been recorded, vaccine status was very poorly recorded, and we were not able to explore many of the possible vaccine failures. Weight-for-height is a better marker of malnutrition than weight-for-age, but few children had their height measured. Some children with low weight-for-age Z-scores might have been born pre-term, which might be a marker of low birthweight or pre-term delivery, not adequacy of post-natal nutrition. Most of the clinically diagnosed cases were not laboratory-confirmed. Dermatologists reviewing children admitted with severe measles at another hospital in Cape Town during the epidemic found a high correlation between clinically-suspected measles and laboratory-confirmed measles. However, this might not apply to clinical diagnosis of mild disease in outpatients.[18]

## Conclusion

The 2009 - 2010 measles outbreak was associated with a large case-load, and high morbidity and mortality at RXH; >65% of the admissions were for children aged <9 months. Measles is a preventable disease, given sufficient political will for the interruption of measles transmission. Vaccine coverage must urgently be improved and supplementary immunisation activities to under-serviced communities be targeted. HIV-infected children had significantly higher case fatality and risk of re-admission. Prevention of vertical transmission of HIV is a national priority, coverage of these programmes must be extended, and early infant HIV diagnosis and treatment should be improved.

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