Diagnostic Utility of Chest X-rays in Childhood Community Acquired Pneumonia in the Era of Bacterial Conjugate Vaccines, Antiretroviral Therapy, Molecular Diagnostics and Computer Aided Diagnosis

Nasreen Mahomed

Student Number: 9701757M

A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the Degree of Doctor of Philosophy in the branch of Medicine: Diagnostic Radiology

Johannesburg, 2017

DECLARATION

I, Nasreen Mahomed, declare that this research thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the School of Clinical Medicine (Diagnostic Radiology) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

Signature of Candidate

6 June 2017

Date

Publications Arising from this Research

Mahomed N, Madhi SA. Radiologic diagnosis of chest infection in children: WHO end-point consolidation. Pediatr Radiol. 2014 Jun; 44(6):685-6. Refer Appendix 1.

Conference Presentations Arising from this Research

7th International Pediatric Radiology (IPR) Conjoint Meeting & Exhibition, 15-20 May 2016, Chicago, Illinois

Three oral presentations:

7th International Pediatric Radiology (IPR) Conjoint Meeting & Exhibition, 15-20 May 2016, Chicago, Illinois. **Mahomed N,** Moore D, Sewchuran T, Moodley H, Madhi S A. Chest X-ray Findings in Children Hospitalized with WHO-Defined Severe, Very Severe Pneumonia in a High HIV Prevalence Setting in the Era of Bacterial Conjugate Vaccines. (PA-137)

7th International Pediatric Radiology (IPR) Conjoint Meeting & Exhibition, 15-20 May 2016, Chicago, Illinois. **Mahomed N**, Moore D, Sewchuran T, Moodley H, Madhi S A. Are Chest X-ray Patterns Associated with Specific Clinical and Acute Phase Reactants in HIV-infected, HIV-Exposed-Uninfected (HEU) and HIV-Unexposed Children Hospitalized with WHO-Defined Severe, Very Severe Pneumonia? (PA-082)

7th International Pediatric Radiology (IPR) Conjoint Meeting & Exhibition, 15-20 May 2016, Chicago, Illinois. **Mahomed N,** Van Ginneken B, Philipsen R, Melendez J, Moore D, Sewchuran T, Moodley H, Madhi S A. Computer Aided Diagnosis (CAD4WHOKids) for WHO Primary Endpoint Pneumonia on Chest X-Ray in Children. (PA-135)

10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD), 26-30 June 2016 Glascow, Scotland

Two oral electronic poster presentations: Ongoing Challenges of Pneumococcal Pneumonia:

10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD),26-30 June 2016 Glascow, Scotland. **Mahomed N**, Moore D, Sewchuran T, Moodley H, Madhi S A. Chest X-ray Findings in Children Hospitalized with WHO-Defined Severe, Very Severe Pneumonia in a High HIV Prevalence Setting in the Era of Bacterial Conjugate Vaccines. (Poster 513)

10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD),26-30 June 2016 Glascow, Scotland. **Mahomed N,** Van Ginneken B, Philipsen R, Melendez J, Moore D, Sewchuran T, Moodley H, Madhi S A. Computer Aided Diagnosis (CAD4WHOKids) for WHO Primary Endpoint Pneumonia on Chest X-Ray in Children. (Poster 479)

One poster presentation:

10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD),26-30 June 2016, Glascow, Scotland. **Mahomed N**, Moore D, Sewchuran T, Moodley H, Madhi S A. Are Chest X-ray Patterns Associated with Specific Clinical and Acute Phase Reactants in HIV-infected, HIV-Exposed-Uninfected and HIV-Unexposed Children Hospitalized with WHO - Defined Severe, Very Severe Pneumonia? (Poster 512)

University of the Witwatersrand, Faculty of Health Sciences Research Day & Postgraduate Expo, 1 September 2016

One oral presentation: Theme 1: Clinical Sciences and Therapeutics for Health

University of the Witwatersrand, Faculty of Health Sciences Research Day & Postgraduate Expo, 1 September 2016. **Mahomed N,** Van Ginneken B, Philipsen R, Melendez J, Moore D, Sewchuran T, Moodley H, Madhi S A. Computer Aided Diagnosis for WHO Chest X-Ray Primary Endpoint Pneumonia in Children. (CS/TH-O-13)

Awarded Best Oral Presentation in Theme 1; refer Appendix 2 for certificate.

One poster presentation: Theme 4: Infectious Diseases

University of the Witwatersrand, Faculty of Health Sciences Research Day & Postgraduate Expo, 1 September 2016. **Mahomed N**, Moore D, Sewchuran T, Moodley H, Madhi S A. Chest X-ray Findings in Children Hospitalized with WHO-Defined Severe Pneumonia in a High HIV Prevalence Setting in the Era of Bacterial Conjugate Vaccines. (ID-P-37)

Acknowledgements

I would like to acknowledge my supervisors, collaborators, organizations and funders:

Supervisor: S A Madhi

Co-supervisor: D P Moore

Chest X-ray Readers: T Sewchuran and H Moodley

Chest X-ray Quality Assurance External Reader: V Manduku

PERCH Core Team, Johns Hopkins Bloomberg School of Public Health, USA: C Prosperi, M Higdon, Z Wu, Q Shi, M Deloria-Knoll, W Gong, N Fancourt, M Knoll, D Park and K O'Brien

Computer Aided Diagnosis International Collaborators: Diagnostic Image Analysis Group, Radboud UMC, Nijmegen, The Netherlands, B van Ginneken, J Melendez, R Philipsen

Chest X-ray Quality Assurance International Collaborators: S Andronikou , T Hlabangana, S Thamthitiwat (Thailand), L Hossain (Bangladesh), L Mwananyanda (Zambia), E Bernard (The Gambia), M Silaba (Kenya), M Tapia (Mali)

MRC Respiratory and Meningeal Pathogens Research Unit (RMPRU): N Ebrahim, F Seedat

Funders: Carnegie PhD Fellowship (Grant number: B8749.R01) administered by the University of Witwatersrand, J Pettifor and B Kramer and Discovery Foundation Academic Fellowship (Reference: 026555)

Abstract

Introduction: Pneumonia is among the leading infectious causes of morbidity and mortality in children under 5 years globally. The chest X-ray remains the most readily available and most common imaging modality for the assessment of childhood pneumonia**.** Chest X-ray quality assurance is important to maintain high image quality, allowing for more accurate diagnosis. Chest X-ray patterns in a high HIV prevalence setting in children hospitalized with pneumonia in the era of bacterial conjugate vaccines has not been described. Furthermore the association between chest X-ray findings and microbiological etiology using novel models is important. Standardization of chest X-ray interpretation is important to allow comparison of research findings between studies and has been proposed by the World Health Organisation (WHO) as a measure of bacterial vaccine efficacy (VE). The role of Computer Aided Diagnosis (CAD) for chest X-ray interpretation is important, especially in countries with limited radiologists.

Objectives: In this thesis we investigated the quality of chest X-rays and the impact of quality assurance activities in the Pneumonia Etiology Research for Child Health (PERCH) study, from 9 sites in 7 countries (Bangladesh, the Gambia, Kenya, Mali, South Africa, Thailand and Zambia), by quantifying radiographic errors through use of a customized quality assessment form. Within the context of the PERCH South African site, we compared chest X-ray patterns in HIV-unexposed, HIV- exposed-uninfected (HEU) and HIV-infected children hospitalized with WHO-defined severe or very severe community acquired pneumonia. Further, we evaluated the association of chest X-ray patterns with clinical parameters and its association with the PERCH Quantitative Analysis (PQA) model predicted probability of infection by a class or specific pathogens. Lastly, we evaluated the utility of CAD for identifying chest X-ray primary end-point

pneumonia (CXR-PEP) versus non CXR-PEP compared to a consensus human interpretation as a reference standard.

Results: A total of 747 chest X-rays in 9 PERCH sites had chest X-ray quality assessment. Collimation performed the worse of the 6 parameters, with 5 out of the 9 sites being graded sub-optimally for this. Three of the 9 sites showed a significant improvement in chest X-ray quality using a test for trend analysis. At the South African PERCH site, 920 cases were enrolled over two years, including 858 children with interpretable chest X-rays. The commonest finding was CXR-PEP, prevalent among 38% HIV-unexposed children, 33% HEU children and 60% of HIV-infected children, which was consistent between different age categories. CXR-PEP was twice as common in HIV-infected (OR 2.5; 95% CI 1.6-3.8) compared with these HIV-unexposed children. Clinical and laboratory features independently associated with CXR-PEP included the presence of severe malnutrition, fever and CRP $\geq$ 40mg/dL. CXR-PEP was associated with the composite outcome of mechanical ventilation or death. However there was no single clinical or laboratory parameter that had both high sensitivity and specificity to discriminate between CXR-PEP from non CXR-PEP cases. HIV-unexposed children with a PQA model probability index $\geq$ 0.5 for bacterial etiology had 2-fold greater odds (95% CI 1.1-4.1) for CXR-PEP compared to non CXR-PEP, and similarly HIV-unexposed children with microbiologically confirmed pneumococcal pneumonia (MCPP) had 3-fold greater odds (95% CI 1.3-6.7) of CXR-PEP. HIV-infected children with a PQA model probability index $\geq$ 0.5 for respiratory viral etiology and PQA model probability index $\geq$ 0.5 for *Pneumocystis jiroveci* etiology trended to have a greater odds for CXR-PEP vs non CXR-PEP.

Using CAD4WHOKids for the 858 interpretable chest X-rays, for CXR-PEP versus non CXR-PEP, CAD4WHOKids had a sensitivity of 76%, specificity of 80% and area under the ROC curve of 0.850 (95% CI 0.823-0.876) compared to the radiologist consensus reading.

Conclusion: Chest X-ray quality, in particular collimation was suboptimal in 7 resource limited countries, in children hospitalized for WHO defined severe or very severe pneumonia. CXR-PEP remains the most common chest X-ray abnormality in HIV-unexposed, HEU and HIV-infected children under 5 years of age hospitalized for WHO-defined severe or very severe pneumonia, even in the era of routine HiB and PCV immunization. Our findings support the literature that CXR-PEP is of limited use in HIV-infected children as an outcome measure in bacterial VE studies, due to opportunistic infections like *Pneumocystis jiroveci* pneumonia and respiratory viral infections contributing to CXR-PEP. CAD is promising as a diagnostic tool for identifying WHO defined CXR-PEP in bacterial VE trials and pneumonia epidemiological studies.

List of Abbreviations

AIDS	acquired immunodeficiency syndrome
ALARA	as low as reasonably achievable
aOR	adjusted odds ratio
AP	anterior posterior
ART	antiretroviral therapy
ASM	active shape model
bpm	breaths per minute
CAD	computer aided diagnosis
CAP	community acquired pneumonia
CHBAH	Chris Hani Baragwanath Academic Hospital
CXR-PEP	chest X-ray primary end-point pneumonia
CI	confidence interval
CRP	C-reactive protein
CRES	Chest Radiography in Epidemiological Studies
Ct	cycle threshold
CT	computerized tomography
DICOM	Digital Imaging and Communications in Medicine
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
ETT	endotracheal tube aspirate
EPI	expanded programme on immunisation
Hib	*Haemophilus influenzae* type b
HibCV	Hib conjugate vaccine

HEU	HIV-exposed, uninfected
HREC	Human Research Ethics Committee
IPD	invasive pneumococcal disease
IS	induced sputum
JPEG	Joint Photographic Experts Group
K	kappa
kVp	kilovolt peak
LA	lung aspirate
LCWI	lower chest wall in drawing
LIP	lymphocytic interstitial pneumonitis
LytA	pneumolysin
MAC	Medical Advisory Board
MAS	milliampere-seconds
MCPP	microbiologically confirmed pneumococcal pneumonia
MTB	*mycobacterium tuberculosis*
NHLS	National Health Laboratory Service
NP	nasopharyngeal
NPOP	nasopharyngeal-oropharyngeal
OR	odds ratio
PACS	picture archiving computerized system
PBP	presumed bacterial pneumonia
PCR	polymerase chain reaction
PCT	procalcitonin
PCV	pneumococcal conjugate vaccine
PCV-7	7-valent pneumococcal conjugate vaccine
PCV-9	9-valent pneumococcal conjugate vaccine

PERCH	Pneumonia Etiology Research for Child Health
PhD	Doctor of Philosophy
PIDS/IDSA	Pediatric Infectious Diseases Society and Infectious Diseases Society of America
PJP	*Pneumocystis jiroveci pneumonia*
PLCM	Partially Latent Class Model
PQA	PERCH Quantitative Analysis
PTB	pulmonary tuberculosis
ROC	receiver operating characteristic
ROI	regions of interest
RR	respiratory rate
RR	relative risk
TB	tuberculosis
VE	Vaccine Efficacy
WCC	white cell count
WHO	World Health Organization
WFPI	World Federation of Paediatric Imaging

TABLE OF CONTENTS

DECLARATION ii
Publications Arising from this Research iii
Conference Presentations Arising from this Research iii
Acknowledgements vi
Abstract vii
List of Abbreviations x
TABLE OF CONTENTS xiii
List of Tables xix
List of Figures xxiii
Preface xxv
PhD Students, N Mahomed Contributions xxvi
1 Introduction 1
2 Literature Review 3
2.1 Literature Review of Quality Assurance of paediatric chest X-rays 3
2.2 Literature Review on the Clinical Impact of HIV on Childhood Community Acquired Pneumonia 4
2.2.1 The Impact of HIV on Pulmonary TB 5
2.2.2 HIV Exposure as a Risk Factor for Childhood Morbidity and Mortality 6
2.3 WHO Standardized Chest X-ray Interpretation for Pneumonia Epidemiological studies and Vaccine Efficacy Trials in Children 7
2.4 Critical Literature Review of Chest X-ray Findings in Childhood Community Acquired Pneumonia 9
2.4.1 Chest X-rays Findings in Children hospitalized with CAP 10
2.4.2 Chest X-rays Findings in HIV-infected Children hospitalized with CAP 10
2.4.3 Chest X-rays Findings in HIV Exposed Uninfected (HEU) Children hospitalized with Community Acquired Pneumonia 11
2.5 Critical Literature Review of Chest X-ray Pattern Association with Acute Phase Reactants and Clinical Signs in Childhood Community Acquired Pneumonia 12
2.5.1 Literature Demonstrating an Association between Acute Phase Reactants, Clinical and Chest X-ray Patterns in Childhood Pneumonia 12
2.5.2 Literature Demonstrating No Association between Acute Phase Reactants, Clinical and Chest X-ray Changes in Childhood Pneumonia 13
2.5.3 Extent of Radiographic Pneumonia and Disease Severity 14

2.6 Critical Literature Review of Chest X-ray Pattern Association with Microbiological Etiology in Childhood Community Acquired Pneumonia 15
2.6.1 Chest X-ray Findings in Children with Pulmonary TB 23
2.6.2 Chest X-ray Findings in *Pneumocystis jiroveci* Pneumonia 24
2.6.3 Chest X-ray Findings in HIV-infected Children in a Chronic Setting 25
2.6.4 Chest X-ray Association with Immune-suppression in HIV-Infected Children 26
2.7 Computer Aided Diagnosis for WHO Standardized Chest X-ray Interpretation for Pneumonia Epidemiological studies and Vaccine Efficacy Trials in Children 27
2.7.1 Limitations of WHO Standardized Chest X-rays Interpretation for Vaccine Efficacy Trials and Pneumonia Epidemiological studies in Children 27
2.7.2 WHO Chest Radiography in Epidemiological Studies (CRES) project 28
2.7.3 Critical Literature Review of Computer-Aided Diagnosis of Chest X-rays 29
2.7.4 Critical Literature Review of Computer Aided Diagnosis of Chest X-rays in Children 31
2.7.5 Limitations of Computer Aided Diagnosis of Chest X-rays 32
3 Rationale for this Study 34
4 Aim and Objectives of this PhD thesis 38
4.1 Aim of this PhD research 38
4.2 The objectives of this PhD research were: 38
5 Methods and Materials 40
5.1 Study setting: The PERCH Study 40
5.1.1 Study Setting: The PERCH Study South African Site 40
5.2 Inclusion and Exclusion Criteria of the PERCH study 41
5.2.1 Inclusion criteria: 41
5.2.2 Exclusion criteria: 42
5.3 Community Controls 42
5.4 Data Centralization 42
5.5 Enrolment of cases in each of the 7 country PERCH study 43
5.6 Methods: To assess the quality of chest X-rays in each of the 7 countries in PERCH study and determine the impact of quality assurance activities 43
5.6.1 Detailed Description of the Radiology Departments in each of the 7 country, 9 site PERCH Study 43
5.6.2 Study Period for Chest X-Ray Quality Assessment in Nine Site PERCH Study 46
5.6.3 Rationale for Frontal and Lateral Chest X-Rays performed in Johannesburg 46
5.6.4 Monthly Uploading Procedures of Chest X-Rays, and Selection of Chest X-Rays for Quality Assessment 46

5.6.5 Customized Chest X-ray Quality Assessment 47
5.6.6 Chest X-ray Quality Assurance Activities at Each of the 9 Sites in Response to the Feedback 48
5.6.7 Chest X-Ray Quality Assessment Scoring System 50
5.6.8 Statistics for Chest X-Ray Quality Assessment 50
5.6.9 Ethics for Chest X-Ray Quality Assessment in the PERCH study 50
5.7 Detailed Description of the X-Ray Units in Paediatric Radiology at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg 51
5.8 Staffing in Paediatric Radiology at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg 52
5.9 Chest X-ray Imaging Procedures of Children at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg 52
5.10 Chest X-Ray Storage and Archiving at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg 53
5.11 Detailed Chest X-Ray Interpretation using the Fleishner chest X-ray glossary of terms and WHO standardized chest X-Ray definitions 53
5.12 Distribution of air space disease and other infiltrate 57
5.13 Chest X-Ray Independent Reading Procedures 58
5.14 HIV Exposure Definitions 58
5.14.1 HIV-infected Children Immune categorization 60
5.15 Clinical history, Clinical findings, laboratory tests, acute phase reactants and poor clinical prognostic outcomes definitions used in this study 61
5.15.1 Clinical History 61
5.15.2 Clinical Findings 62
5.15.3 Acute phase reactants 63
5.15.4 Poor clinical prognostic outcomes: 64
5.16 Specific Pathogens Investigated in PERCH 65
5.17 The PERCH Quantitative Analysis (PQA) Model 66
5.18 Microbiologically Confirmed Pneumococcal Pneumonia (MCPP) 67
5.19 *Pneumocystis jiroveci* testing 67
5.20 Pulmonary TB 68
5.20.1 Mycobacterium tuberculosis culture 68
5.20.2 Pulmonary TB 68
5.20.3 Culture or clinical Pulmonary TB 68
5.20.4 Non-TB Cases 68

5.21 Data analysis and statistics for objectives 2 to 5 69
5.22 Ethics 70
5.23 Funding 70
6 Objective 1: Chest X-ray Quality Assurance in the 7 country PERCH Study: Results, Discussion, Limitations 71
6.1 Results 71
6.1.1 Number of Chest X-rays with Quality Assurance Assessment in Each Site 71
6.1.2 Chest X-Ray Quality Assessment in Each of the Six Parameters for Each Site 72
6.1.3 Combined Nine Site Assessment 77
6.1.4 Chest X-ray Quality Time Series Analysis using Test for Trend 77
6.2 Discussion: Objective 1 79
6.3 Study Limitations: Objective 1 83
6.4 Recommendations from this Study to Obtain Good Quality Chest X-rays with Dose Optimization in Developing Countries without Paediatric Radiographers and Paediatric Trained Radiologists 85
7 Objective 2: Chest X-ray patterns by HIV-exposure Status: Results, Discussion, Limitations 87
7.1 Results 87
7.1.1 Interpretable Chest X-rays 87
7.1.2 Demographic Data 87
..... 89
7.1.3 Chest X-Ray Findings in Children Hospitalized for WHO-defined Severe or very Severe Pneumonia, Stratified by HIV Status 90
7.1.4 Chest X-ray findings in Children Hospitalized for WHO-defined severe or very severe pneumonia, Stratified by Age Category and HIV status 96
7.1.5 Chest X-ray patterns Stratified by HIV Status and Age Categories 109
7.1.6 Distribution of airspace disease and other infiltrate on chest X-ray 109
7.2 Discussion: Objective 2 112
7.3 Limitations: Objective 2 117
7.4 Future Research: Objective 2 117
8 Objective 3: Chest X-ray Patterns by Clinical Parameters: Results, Discussion, Limitations 118
8.1 Clinical Results 118
8.1.1 Results: The association of chest X-ray patterns with clinical symptoms and signs, HIV exposure status, acute phase reactants and clinical outcomes 126
8.1.2 Chest X-Ray Primary End Point Pneumonia (CXR-PEP) vs no Chest X-Ray Primary End Point Pneumonia (CXR-PEP) 126

8.1.3 Other Infiltrate Only vs no other Infiltrate only 127
8.1.4 Intrathoracic Lymphadenopathy vs no intrathoracic lymphadenopathy 128
8.1.5 Bilateral air trapping vs no bilateral air trapping 128
8.1.6 Chronic Lung Disease vs no chronic lung disease 129
8.1.7 Normal chest X-ray vs any chest X-ray changes 130
8.1.8 Sensitivity and specificity of clinical history, clinical findings, acute phase reactants and poor clinical prognostic outcomes in predicting CXR-PEP compared to cases without CXR-PEP in HIV-unexposed, HIV-exposed, uninfected and HIV-infected children hospitalized with WHO-defined severe or very severe pneumonia 137
8.2 Discussion: Objective 3 139
8.3 Limitations: Objective 3 142
9 Objective 4: Chest X-ray Pattern Association with Microbiological Etiology: Results, Discussions, Limitations 144
9.1 Summary of Methods 144
9.2 Results: 145
9.2.1 Etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB for each HIV exposure group 145
9.2.2 Chest X-Ray Primary End Point Pneumonia (CXR-PEP) association with microbiological etiology 147
9.2.3 Sensitivity, Specificity of CXR-PEP in predicting microbiological etiology based on PERCH Quantitative Analysis model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed PTB 148
9.2.4 Other Infiltrate only association with microbiological etiology 153
9.2.5 Thoracic lymphadenopathy association with microbiological etiology 155
9.2.6 Chest X-ray chronic lung disease association with microbiological etiology 157
9.2.7 Bilateral Air Trapping association with microbiological etiology 159
9.2.8 Normal chest X-ray compared to any chest X-ray changes association with microbiological etiology 161
9.3 Discussion: Objective 4 163
9.4 Limitations: Objective 4 168
9.5 Future Research on Chest X-ray Findings and Microbiological Etiology 170
10 Objective 5: Chest X-ray Patterns and Computer Aided Diagnosis: Methods, Results, Discussion, Limitations 171
10.1 Methods 171
10.1.1 International Collaboration 171

10.1.2 Study Setting- PERCH Study, South Africa 172
10.1.3 Summary of Chest X-ray Findings 172
10.1.4 Computer Aided Diagnosis (CAD4WHOKids) of Chest X-Rays in Children 172
10.1.5 Data Analysis 176
10.1.6 Budget 176
10.2 Results 177
10.2.1 Computer Aided Diagnosis for CXR-PEP vs non CXR-PEP Compared to Consensus Radiologist Reading Reference Standard 177
10.2.2 Computer Aided Diagnosis for CXR-PEP vs Other Infiltrate Only Compared to Consensus Radiologist Reading Reference Standard 178
10.2.3 Colour Heat Map on Chest X-ray 179
10.2.4 Computer Aided Diagnosis vs Independent Human Reading 180
10.2.5 Computer Aided Diagnosis on Chest X-ray, Analysis by HIV exposure status 181
10.3 Discussion: Objective 5 183
10.4 Limitations: Objective 5 185
10.5 Future Work on Computer Aided Diagnosis on chest X-ray-CAD4WHOKids 186
11 Conclusion of this PhD Thesis 188
11.1 Objective 1 188
11.2 Objective 2, 3 and 4 189
11.3 Objective 5 192
11.4 Unifying Conclusion 192
12 References 195
13 Appendices 204
13.1 Appendix 1: Radiologic diagnosis of chest infection in children: WHO end-point consolidation 204
13.2 Appendix 2: Best Oral Paper University of the Witwatersrand, Faculty of Health Sciences Research Day & Postgraduate Expo, 1 September 2016, Theme 1: Clinical Sciences and Therapeutics for Health 206
13.3 Appendix 3: Chest X-Ray Quality Assessment Customized Report Form 207
13.4 Appendix 4: Customized Detailed Chest X-Ray Reporting Form 210
13.5 Appendix 5: Wits HREC Certificate for this Study 213
13.6 Appendix 6: Wits HREC for the PERCH Study, South African Site 214
13.7 Appendix 7: CHBAH MAC Permissions for the PERCH Study, South African Site 215
13.8 Appendix 8 Report from Turnitin 216

List of Tables

Table No	Table Heading	Page No
2.1	WHO Standardized Chest X-ray Interpretation in Children for the Diagnosis of Pneumonia in Epidemiological Studies	8-9
2.2	Review of Selected Studies on Chest X-ray Findings in Hospitalized Children with Community Acquired Pneumonia	18
2.3	Review of Selected Studies of Chest X-Ray Pattern Association with Clinical Parameters in Childhood Community Acquired Pneumonia	19-20
2.4	Review of Selected Studies of Chest X-ray Pattern Association with Microbiological Etiology in Childhood Community Acquired Pneumonia	21-22
5.1	WHO-Defined Clinical Criteria for Severe and Very Severe Pneumonia	41
5.2	Detailed Description of the Radiology Departments in each of the 7 country, 9 site PERCH Study	45
5.3	Customized Chest X-ray Quality Assessment	47-48
5.4	Chest X-ray Quality Assurance Activities at Each of the 9 Sites in Response to the Feedback	49
5.5	Detailed Description of Radiography Units used for Children at Chris Hani Baragwanath Academic Hospital	51
5.6	Chest X-Ray Pattern and descriptors used in this study	56-57
5.7	HIV exposure and infection categorization	59-60
5.8	WHO immunological classification HIV-infected children 0- 59 months	61
5.9	Standardized Clinical Findings Definitions used in this study	63
5.10	Standardized acute phase reactants definitions used in this study	64
5.11	Poor clinical prognostic outcomes definitions	64

Table No	Table Heading	Page No
6.1	Number and percentage of Chest X-rays with Quality Assessment in Each Site	72
6.2	Combined Nine Site Results for each of the 6 Chest X-Ray Quality Assessment Parameters	77
6.3	Chest X-ray Quality Time Series Analysis over 14 month period for each of the 9 sites using Test for Trend	78
6.4	Site Specific Limitations and challenges in optimizing chest X-ray quality	84-85
7.1	Chest X-ray findings in Children hospitalized for WHO-defined severe or very severe pneumonia, Stratified by HIV Status	93-95
7.2	Chest X-ray findings in Infants 1-5 months (age category 1), hospitalized for WHO-defined severe or very severe pneumonia, stratified by HIV status	100-102
7.3	Chest X-ray findings in Children 6-11 months (age category 2),hospitalized for WHO-defined severe or very severe pneumonia, stratified by HIV status	103-105
7.4	Chest X-ray findings in Children 12-59 months (age category 3), hospitalized for WHO-defined severe or very severe pneumonia, stratified by HIV status	106-108
7.5	Chest X-Ray findings in Children hospitalized for WHO-defined severe or very severe pneumonia Analysed by HIV Exposure Status and Age Categories	110
7.6	Chest X-ray Pattern distribution of air space disease and other infiltrate in each age category, in children hospitalized for WHO-defined severe or very severe pneumonia	111
8.1	Demographic, clinical and laboratory features of infants 1-5 months of age hospitalized for severe or very severe pneumonia, stratified by HIV Status	120-121
8.2	Demographic, clinical and laboratory features of children 6-11 months of age hospitalized for severe or very severe pneumonia, stratified by HIV Status	122-123

Table No	Table Heading	Page No
8.3	Demographic, clinical and laboratory features of Children 12-59 months of age hospitalized for severe or very severe pneumonia, stratified by HIV Status	124-125
8.4	Chest X-ray primary end-point pneumonia (CXR-PEP) and Other infiltrate only association with clinical parameters, HIV exposure status, acute phase reactants and poor prognostic outcomes in children hospitalized with WHO-defined severe or very severe pneumonia	131-132
8.5	Chest X-ray thoracic lymphadenopathy and bilateral air trapping association with clinical parameters, HIV exposure status, acute phase reactants and poor prognostic outcomes in children hospitalized with WHO-defined severe or very severe pneumonia	133-134
8.6	Chest X-ray patterns of chronic lung disease and Normal chest X-ray association with clinical parameters, HIV exposure status, acute phase reactants and poor prognostic outcomes in children hospitalized with WHO-defined severe or very severe pneumonia	135-136
8.7	Sensitivity and specificity of clinical findings, acute phase reactants and poor clinical outcomes in predicting Chest X-Ray Primary End-Point Pneumonia (CXR-PEP) in HIV-unexposed, HIV-exposed uninfected and HIV-infected children hospitalized with WHO-defined severe or very severe pneumonia	138
9.1	Microbiological Etiology in Children hospitalized for WHO-defined severe or very severe pneumonia based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	146
9.2	Chest X-Ray primary end point pneumonia (CXR-PEP) association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	151
9.3	Sensitivity, Specificity of CXR-PEP vs non CXR-PEP in predicting microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	152
9.4	Other Infiltrate only association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	154

Table No	Table Heading	Page No
9.5	Thoracic lymphadenopathy association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	156
9.6	Chest X-Ray chronic lung disease association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	158
9.7	Bilateral Air Trapping association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	160
9.8	Normal chest X-ray association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB	162

List of Figures

Figure No	Figure Heading	Page No
6.1	Bar Graph demonstrating Positioning results in each of the 9 sites	74
6.2	Bar Graph demonstrating Collimation results in each of the 9 sites	74
6.3	Bar Graph demonstrating Exposure results in each of the 9 sites	75
6.4	Bar Graph demonstrating Motion results in each of the 9 sites	75
6.5	Bar Graph demonstrating Inspiration results in each of the 9 sites	76
6.6	Bar Graph demonstrating Processing results in each of the 9 sites	76
7.1	Availability of chest X-rays in children 1-59 months hospitalised for WHO-defined severe or very severe pneumonia and associated HIV-exposure and infection status	89
10.1	ROC curve (with 95 % CI) for CXR-PEP vs non CXR-PEP from the 858 chest X-rays CAD4WHOKids had a sensitivity of 76%, specificity of 80% and area under the ROC curve of 0.850 (95% CI 0.823-0.876) using the radiologist consensus reading as the reference standard	177
10.2	ROC curve (with 95% CI) for CXR-PEP vs other infiltrate only, from 541 chest X-rays CAD4WHOKids had a sensitivity of 77%, specificity of 73%, and area under the ROC curve of 0.810 (95% CI 0.772-0.846) using the radiologist consensus reading as the reference standard	178
10.3	Colour Heat Map: to visualise the working of the texture system, for each image a colour heat map was generated with red representing high likelihood of being abnormal, yellow intermediate, green low, and blue very low. The 2 examples represented here demonstrate good correlation between the areas of CXR-PEP and the results of the software CAD4WHOKids colour heat map and on the test chest X-rays	179
10.4	ROC curve with 95% CI from 200 randomly selected chest X-rays, comparing independent scoring system by the principle investigator for CXR-PEP versus non CXR-PEP and the CAD4WHOKids system	180

Figure No	Figure Heading	Page No
10.5	ROC curve (with 95% CI) for CXR-PEP vs non CXR-PEP in 428 HIV-unexposed children. CAD4WHOKids had a sensitivity of 80%, specificity of 76% and area under the ROC curve of 0.845 (95% CI 0.806 – 0.881) using the radiologist consensus reading as the reference standard	181
10.6	ROC curve (with 95% CI) for CXR-PEP vs non CXR-PEP in 284 HEU children. CAD4WHOKids had a sensitivity of 80%, specificity of 75% and area under the ROC curve of 0.850 (95% CI 0.801-0.895) using the radiologist consensus reading as the reference standard	182
10.7	ROC curve (with 95% CI) for CXR-PEP vs non CXR-PEP in 108 HIV-infected children. CAD4WHOKids had a sensitivity of 75%, specificity of 77% and area under the ROC curve of 0.814 (95% CI 0.726-0.892) using the radiologist consensus reading as the reference standard	183

Preface

This thesis is presented using the recommended University of the Witwatersrand "divided block" format. In this format the thesis consists of an **Introduction** (chapter 1), **Literature Review** (chapter 2), **Rationale for this Study** (chapter 3), Aims and Objectives (chapter 4) and **Methodology** (chapter 5).

The Results, Discussion and Limitations of each of the 5 objectives are presented as individual chapters, as per the divided block thesis format. Objective 1 is nested within the 7 country Pneumonia Etiology Research for Child Health (PERCH) study, and objectives 2 to 5 are nested within the PERCH study, South African site. **Objective 1** Quality of chest X-rays in each of the 7 country Pneumonia Etiology Research for Child Health (PERCH) study consists of Results, Discussion, Limitations (chapter 6). **Objective 2** To describe and compare chest X-ray patterns the in HIV-unexposed, HIV- exposed-uninfected (HEU) and HIV-infected children 28 days to 59 months of age hospitalized with WHO-defined severe or very severe community acquired pneumonia consists of Results, Discussion, Limitations (chapter 7). **Objective 3** To determine the association of chest X-ray patterns with clinical symptoms and signs, HIV exposure status, acute phase reactants and clinical outcomes in children hospitalized with WHO-defined severe or very severe community acquired pneumonia consists of Results, Discussion, Limitations (chapter 8). **Objective 4** To determine the association of specific chest X-ray patterns and microbiological etiology consists of Results, Discussion, Limitations (chapter 9). **Objective 5** To determine the sensitivity and specificity of computer aided diagnosis for chest X-ray primary end-point pneumonia (CXR-PEP) versus non CXR-PEP consists of Methods, Results, Discussion, Limitations (chapter 10). The final chapters consist of the **Conclusion of this thesis** (chapter 11), **References** (chapter 12) and **Appendices** (chapter 13).

PhD Students, N Mahomed Contributions

Dr Mahomed conceptualized all the objectives of her PhD and obtained ethics approval for her PhD. Dr Mahomed is the Paediatric Radiology investigator in the Pneumonia Etiology Research for Child Health (PERCH) study, South African site and was the Head of Paediatric Radiology unit at Chris Hani Baragwanath hospital during the study period. Dr Mahomed contributed to the site specific South African PERCH protocol and assisted the lead clinician Dr Moore with chest X-ray data collection, collation and troubleshooting during the 2 year prospective study period (17 August 2011 to 31 August 2013).

Dr Mahomed was also responsible for chest X-ray quality assurance activities at the South African site during the study. Her proposal for objective 1 on evaluating chest X-ray quality in the 7 PERCH sites was submitted and approved by the PERCH Executive Committee for both the purposes of this PhD thesis and publication. Dr Mahomed communicated directly with the radiology investigators in each of the PERCH sites (6 other countries) for purposes of this objective.

Dr Mahomed is certified in WHO standardized chest X-ray interpretation after completing formal training and assessment in London (UK) in September 2012. Dr Mahomed is also on the WHO Chest Radiography in Epidemiological Studies (CRES) committee and representing the World Federation of Paediatric Imaging (WFPI) on this committee. In addition, she is on the international PERCH chest X-ray reading panel, which consisted of 14 international readers, 2 from each of the 7 PERCH countries. Furthermore, she was responsible for training the 2 local radiologists from South Africa in WHO standardized chest X-ray interpretation as part of the site specific, detailed chest X-ray interpretation of this study.

Dr Mahomed spent time working on her PhD in 2015 at the Johns Hopkins Bloomberg School of Public Health, Baltimore, USA, where the central co-ordination of the PERCH Project was undertaken. Dr Mahomed collaborated on the development of the PERCH Quantitative Analysis (PQA) South African specific model, which related to her PhD study during her time at Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

Dr Mahomed conceptualized objective 5, on computer aided diagnosis for WHO-defined chest X-ray interpretation. After reviewing the literature Dr Mahomed approached the Diagnostic Image Analysis Group, from Radboud UMC, Nijmegen, The Netherlands with her proposal for an international collaboration which was accepted. Her collaborators came to Johannesburg, South Africa to work on the study in 2015.

Statistical analyses for all 5 objectives were conducted by Dr Mahomed. Assistance and verification was given by her supervisors and the PERCH Core Team (Ms C Prosperi and Ms M Higdon**)** from Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

Dr Mahomed applied and was awarded 2 research grants Carnegie PhD Fellowship (Grant number: B8749.R01) and Discovery Foundation Academic Fellowship (Reference: 026555) to fund her PhD study.

Dr Mahomed's journal submission of the 5 publications arising from this PhD was limited to the PERCH 7 country primary paper being published. Dr Mahomed attended the PERCH Executive committee meeting on 25 June 2016, Glascow, Scotland. The PERCH primary paper is currently still a work in progress.

1 Introduction

Pneumonia is among the leading infectious causes of morbidity and mortality in children less than 5 years of age globally (1-3). Childhood pneumonia accounted for 18% of deaths in this age group and in developing countries pneumonia accounted for 1.5 million deaths per year (1). *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b (Hib) are the most important causes of vaccine-preventable deaths in children less than 5 years of age, in the absence of vaccination against these pathogens (4, 5). In 2000, before the widespread use of bacterial conjugate vaccines, *S. pneumoniae* caused an estimated 14.5 million cases of pneumococcal disease (95.6% pneumonia) and 826 000 deaths (4) while Hib caused 370 000 deaths (5). Furthermore, recent literature demonstrated that the pneumococcus is estimated to have caused 411,000 and 335,000 deaths globally in 2010 and 2015 respectively, in children less than 5 years of age (6).

Other important causes of childhood bacterial pneumonia include *Staphylococcus aureus, Mycoplasma pneumoniae* and non-typable *Haemophilus influenza*. Furthermore respiratory syncytial virus, human rhinovirus, human metapneumovirus, adenovirus, parainfluenza virus types 1and 3 and influenza A and B are also variably implicated in the pathogenesis of childhood lower respiratory tract infections (LRTI), including pneumonia (7). Respiratory viral infections have also been implicated to increase the susceptibility to bacterial pneumonia (7).

It is recognized that the chest X-ray has a number of limitations compared to imaging modalities like ultrasound chest and computerized tomography (CT) chest in the diagnosis of childhood pneumonia (8-13). However the chest X-ray remains the most readily available and the most

common imaging modality for the assessment and diagnosis of childhood community acquired pneumonia (CAP), especially in lower income countries where CT is not available (14). In 1997 the World Health Organization (WHO) Radiology Working Group was established to provide a consensus method for the standardized interpretation of pediatric frontal chest X-rays, for use in bacterial vaccine efficacy (VE) trials in children; with a focus on reproducible chest X-ray readings, which would allow for "comparison and generalizability of results from one region to another." Standardized definitions on chest X-ray quality were also provided. These definitions and end-point conclusions were published in 2001 and an analysis of observer variation for these conclusions using a reference library of chest X-rays was published in 2005 (15). The conclusion of chest X-ray primary end-point pneumonia (CXR-PEP) was optimized for use as an end-point in bacterial Hib and pneumococcal conjugate vaccine (PCV) vaccine trials and for determining the spectrum of disease burden from pneumonia epidemiological studies in children (15).

In South Africa the PCV demonstrated vaccine efficacy (VE) for chest X-ray confirmed pneumonia , based on WHO standardized interpretation criteria for CXR-PEP (15) of 20% in HIV-uninfected children and 13% in HIV-infected children not on antiretroviral therapy (ART) (16). Similarly, PCV efficacy against CXR-PEP was 37% in The Gambia (17), 30% in USA (18) and 23% in the Philippino children (19). In 2007 the WHO recommended global implementation of the 7-valent pneumococcal conjugate vaccine (PCV -7) into national immunization programs, especially in countries "with under 5 year mortality of >50/1000 live births or where >50 000 children die annually" and in countries with a high HIV prevalence (20).

Therefore it would be important to describe WHO-defined chest X-ray findings in children under 5 years hospitalized with CAP (15), following the introduction of PCV and Hib vaccine in a developing country, like South Africa with a high HIV prevalence and a national ART program.

2 Literature Review

2.1 Literature Review of Quality Assurance of paediatric chest X-rays

Quality assurance of paediatric chest X-rays is a critical means of ensuring and maintaining high image quality as optimized image quality allows for more accurate diagnosis (21-23). Radiation protection is important in children who have more radiosensitive organs and have increased risk for radiation induced cancer compared to adults (21, 22, 24, 25). To achieve this paediatric radiology emphasizes 'diagnostic quality' over 'best quality' (22), with particular emphasis on the dose to be As Low As Reasonably Achievable (ALARA) (26, 27) as emphasized in the Image Gently guidelines and campaigns (27, 28).

Quality assurance of paediatric chest X-rays may be compromised in unsupervised radiology units without paediatric trained radiographers or radiologists (21-23). Cook et al recommend that in the ideal setting quality assurance in radiography should be performed on a continuous daily basis (22); however this is not always possible in resource limited environments (23). Good radiographic technique is the best way to improve quality without actually increasing the dose of radiation (22). Following the guidelines outlined in the ALARA principles, good collimation that only includes the field of interest and the use of protective shielding are essential for dose reduction, although these may result in chest X-ray cut-off or obscuring of important structures by the shield in a very mobile child. To address the issue of mobility of children, radiographers sometimes do the opposite and use wide collimation when children are moving and uncooperative (21). Patient immobilization devices may improve the quality of paediatric chest X-rays in terms of rotation, lordosis and scoliosis but does not have an impact in improving collimation, cut-off and inspiration (29). These devices are recommended for hospitals without paediatric trained radiographers to improve chest X-ray quality (29).

Certain paediatric chest diseases may "mirror radiographic noise", which highlights the need for optimal and consistent image acquisition protocols and practices to enable radiologists and clinicians to differentiate between actual diseases like pneumonia from poor quality chest X-rays (25, 26). Children are smaller in size and often less compliant than adults which affects the manner in which chest X-rays are performed and the methods employed to optimize dose (28). Efforts to reduce dose should not compromise on image quality (28) as paediatric radiographs have relatively low contrast (26). A constant challenge in paediatric radiography is achieving the balance between acceptable image quality and low radiation dosage. Paediatric patients vary in size and weight within the same age group. This necessitates imaging techniques with a range of different parameter settings for the same anatomical regions, to gain optimal results (26). Experienced and dedicated staff are the key to quality imaging in children (22) as staff with greater experience are more capable of selecting imaging parameters that will optimize the quality and limit the radiation dose to the paediatric patient (26).

2.2 Literature Review on the Clinical Impact of HIV on Childhood Community Acquired Pneumonia

According to the UNAIDS Report on the Global Aids Epidemic 2013, approximately 3.3 million children under the age of 15 years are living with HIV infection globally. Sub-Saharan Africa has the highest burden of disease with 2.9 million (88%) of HIV-infected children (30). HIV has affected the epidemiology of childhood pneumonia, including changes in the profile of pathogens causing pneumonia, antimicrobial susceptibility of bacteria and prognostic outcome (31). Studies on HIV-infected children hospitalized with severe pneumonia found *S. pneumoniae*, *S. aureus*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis* (MTB) and

Pneumocystis jiroveci to be more commonly identified etiological agents than in HIV-uninfected children (32). Furthermore the role of poly-microbial infections in the pathogenesis of pneumonia in HIV-infected children has been recognized (32). Antiretroviral therapy has decreased the incidence of opportunistic infections and improved survival in HIV-infected children (33).

HIV-infected children have an increased risk of developing invasive pneumococcal disease (IPD) including bacteraemic pneumonia (31). A South African study conducted in the pre- PCV era demonstrated that the burden of severe IPD was 42 fold (95% confidence interval (CI) 26.5-65.6) higher in HIV-infected children compared to HIV-uninfected children less than 2 years of age. Furthermore, HIV-infected children had an increased risk of infections caused by multi-drug resistant organisms, including penicillin and trimethoprim-sulfamethoxazole (34).

2.2.1 The Impact of HIV on Pulmonary TB

In HIV infected patients, TB is one of the most common opportunist infection, and it is responsible for a third of deaths (35). HIV has increased the incidence of TB in sub-Saharan Africa (36). HIV-infected children have an increased risk of developing progressive pulmonary TB (PTB) or disseminated TB compared to HIV-uninfected children (37). The burden of hospitalization for culture-confirmed tuberculosis (TB) was 42-fold greater among HIV-infected children compared with HIV-uninfected children in 2009. The majority (78%) of HIV-infected TB cases were severely immunocompromised (38), supporting literature that the risk of TB disease increases with severe immune suppression (37). A PCV-probe study in South Africa suggested that in a setting with high HIV and TB prevalence, hospitalization in children with culture-confirmed PTB was often precipitated by pneumococcal co-infection (39).

2.2.2 HIV Exposure as a Risk Factor for Childhood Morbidity and Mortality

Globally there have been improved strategies to prevent mother-to-child transmission of HIV infection (40). Hence HIV-exposed, uninfected (HEU) children may account for a significant proportion, approximately 30% of all births in parts of Southern Africa (40). Due to preventative strategies in South Africa, the mother-to-child transmission of HIV has decreased from 12% in 2007 to 2.5% in 2012-2013 (41).

HEU infants have two-to-four-fold higher mortality compared to HIV-unexposed children in the African setting (42, 43). Respiratory and gastrointestinal infections are the main cause of infant morbidity and mortality in HEU infants (43). Putative causes of increased infant morbidity and mortality in HEU children include impaired infant immunity, low white cell count at birth, advanced maternal HIV disease, poor placental transfer of protective maternal antibodies and increased exposure to pathogens in the home environment (32, 40, 42, 43).

HEU children have increased risk of developing severe pneumonia compared to HIV-unexposed children. Opportunistic infections like *Pneumocystis jiroveci* pneumonia (PJP) have been reported in HEU children (32). HIV-infected children have a 15-fold increased risk of invasive pneumococcal disease hospitalization and a 2-fold risk of death compared with HIV-unexposed children (41). Comparatively HEU children are twice as likely to be hospitalized with invasive pneumococcal disease compared to HIV-unexposed children. HEU children under 6 months are at higher risk of dying (relative risk 1.76) compared with HIV-unexposed children. Younger children may be more susceptible to the immunological differences associated with HIV exposure and after 6 months of age the immunological deficits may be reduced (41).

Vaccine-specific antibody responses were equivalent in HEU children compared with HIV-unexposed children according to the Expanded Programme on Immunization (EPI) vaccination

program (43, 44). HEU responded quantitatively as well compared with HIV-unexposed children for vaccinations in the EPI like tetanus, pertussis, measles, Hib, and hepatitis B (44). PCV was highly effective in HEU children in South Africa when given as part of the EPI (45). However a South African study which interrogated PCV immunogenicity demonstrated that higher antibody concentrations were required for PCV serotypes effectiveness in HEU children (46).

2.3 WHO Standardized Chest X-ray Interpretation for Pneumonia Epidemiological studies and Vaccine Efficacy Trials in Children

The chest X-ray remains the most readily available and the most common imaging modality for the assessment and diagnosis of childhood community acquired pneumonia (14). The 2011 Pediatric Infectious Diseases Society and Infectious Diseases Society of America (PIDS/IDSA) guidelines for the management of CAP recommend routine chest X-rays (posterior-anterior and lateral views) for children hospitalized for CAP. Chest X-rays are used to document the presence, type and extent of lung parenchymal infiltrate and identify complications of pneumonia that may need surgical intervention (47). Due to the limited availability of radiologists in low income countries, clinicians often interpret chest X-rays (14, 48). Inter-reader agreement of paediatric chest X-ray readings between clinicians and radiologists for overall radiographic classification is fair to moderate (K=0.21-0.60), while agreement of individual radiographic features is poor (K=0.01-0.20) (49-52).

Standardization of paediatric chest X-ray interpretation is important to improve inter-reader agreement and also to allow comparison of results between studies from different geographic areas (18, 47). Chest X-ray confirmed pneumonia is used as an important outcome measure in pneumonia epidemiological studies and vaccine efficacy trials. In 1997 the WHO developed a Radiology Working Group to provide a consensus method for interpreting chest X-rays in the context of it being used as an endpoint in pneumococcal conjugate vaccine efficacy trials. The

WHO working group proposed that chest X-rays with significant abnormality be classified into 3 main groups: end-point consolidation, other (non-end-point) infiltrate or pleural effusion (15).

End-point consolidation is defined as a "dense or fluffy opacity that occupies either a portion, lobe or entire lung, with or without air bronchograms." Other (non-end-point) infiltrate is defined as "linear, patchy densities (interstitial infiltrate) in a lacy pattern associated with peri-bronchial thickening and atelectasis not sufficient enough to call end-point consolidation". The details of these definitions are described in Table 1.1. The WHO proposed classifying chest X-rays into one of 3 main conclusions: primary end-point pneumonia, other infiltrate, no consolidation/infiltrate/effusion. Primary end-point pneumonia **(CXR-PEP)** is defined as "end-point consolidation or pleural effusion involving the lateral pleural space" and that is "spatially associated with pulmonary parenchymal infiltrate (including other infiltrate) or if the effusion obliterates the hemi-thorax to obscure an opacity." Other infiltrate is defined as the presence of (non-end point) infiltrate in the absence of a pleural effusion. Further details of this WHO standardized chest X-ray interpretation are described in Table 2.1 (15).

Table 2.1 WHO Standardized Chest X-ray Interpretation in Children for the Diagnosis of Pneumonia in Epidemiological Studies (15)

	Chest X-ray Finding	**Radiographic definition**
Classification of Findings	End-point consolidation	dense or fluffy opacity that occupies either a portion, lobe or entire lung, with or without air bronchograms
	Other (non-end point) infiltrate	linear, patchy densities (interstitial infiltrate) in a lacy pattern associated with peri-bronchial thickening and atelectasis not sufficient enough to call end point consolidation. It also includes minor patchy infiltrates that are not of sufficient magnitude to

		constitute primary end-point consolidation, and small areas of atelectasis which in children can be difficult to distinguish from consolidation
	Pleural effusion	fluid in the pleural space in the lateral pleural space, between the lung and chest wall, may be at the costophrenic angle or as a layer adjacent to the lateral chest wall, but not in the horizontal or oblique fissures
Conclusions	**Primary end-point pneumonia**	endpoint consolidation **OR** pleural effusion involving the lateral pleural space associated with pulmonary parenchymal infiltrate (Other infiltrate) **OR** if the effusion obliterates the hemi-thorax to obscure an opacity
	Other infiltrate	the presence of (non-end point) infiltrate in the absence of a pleural effusion
	No consolidation/infiltrate/effusion	absence of end-point consolidation, other infiltrate or pleural effusion

2.4 Critical Literature Review of Chest X-ray Findings in Childhood Community Acquired Pneumonia

Childhood community acquired pneumonia (CAP) is defined as symptoms and signs of pneumonia in a previously healthy child due to infection acquired outside the hospital setting (53). Besides HIV infection (31) and HIV exposure without infection (32, 43), other risk factors associated with the development of childhood CAP include young age (54, 55), lack of breast feeding (56) and malnutrition (57, 58).

2.4.1 Chest X-rays Findings in Children hospitalized with CAP

Chest X-ray abnormalities are common in hospitalized children with CAP (59-62), with air apace/alveolar consolidation the commonest finding 40-75%, followed by interstitial infiltrates 9-54% (59-62). Air space/alveolar consolidation was found to be predominantly unilateral, right sided and lobar in distribution (59-61). Hilar lymphadenopathy has been reported in 23-26% of children in countries with a high TB prevalence (61, 62). Complications such as lung abscess, cavitation, and pneumothorax are reported to be infrequent in childhood CAP (59-62). While Key *et al* (59) and Madhi *et al* (62) both found a high prevalence of hyperinflation (23-42%) (59, 62), a low prevalence of this finding (1%) was reported by Bharti *et al* (61). Key *et al* found that upper lobe changes predicted severity in 65% (59), but Bharti *et al* did not identify an association between chest X-ray findings and clinical outcomes (61). The above findings in addition to other data from the relevant articles are summarised below in Table 2.2 (59-62). Chest X-ray findings of interstitial infiltrate and hyperinflation are more common in children <1 year (59, 60). This is likely due to a greater proportion of childhood CAP being associated with respiratory viruses among infants, whereas bacterial infections are proportionately more common among older children (62-65), (Refer Tables 2.2 and 2.4).

2.4.2 Chest X-rays Findings in HIV-infected Children hospitalized with CAP

Madhi *et al* investigated chest X-ray findings in hospitalized HIV-infected children with CAP in the 1990s, where none of the children were on ART and prior to routine immunization with Hib conjugate vaccine (HibCV) or PCV. The findings from that study established that air space/alveolar consolidation was more common in HIV-infected children compared to HIV-uninfected children. Whereas bronchopneumonia changes and normal chest X-ray were more common in HIV-uninfected children compared to HIV-infected children with clinically diagnosed pneumonia (62), (refer to Table 2.2). Furthermore respiratory viral infections were

more likely to present with air space/alveolar consolidation in HIV-infected children compared to HIV-uninfected children (62), (refer to Table 2.4). This suggests the possibility of a higher prevalence of bacterial and respiratory viral co-infection in HIV-infected children not on ART and in the absence of PCV. Limitations of this study included the use of blood cultures, which had a low sensitivity (3.1-4.7%) for diagnosing bacterial pneumonia, a low prevalence of respiratory viral infections (4.4-11.2%) and children that were not investigated for PJP previously (62). Kelly *et al* investigated chest X-ray findings and pneumonia outcomes in a high HIV prevalence setting in Botswana in children 1-23 months of age, where HiB was introduced in the country's immunization program 2 years before the study enrolment and PCV-13 was introduced 2 months after the study enrolment commenced (66). WHO standardized chest X-ray interpretation criteria was used (15). From 249 children with interpretable chest X-rays, 35% had CXR-PEP and 42% other infiltrate. Nine percent (22/249) of these children were HIV-infected, and HIV-infected children were more likely to have CXR-PEP (64% vs 32%; p=0.004), compared to HIV-uninfected children (66).

2.4.3 Chest X-rays Findings in HIV Exposed Uninfected (HEU) Children hospitalized with Community Acquired Pneumonia

The only published study describing chest X-ray findings in HEU children hospitalized with WHO-defined clinical pneumonia was undertaken in Kwa-Zulu Natal in 2002, which was prior to routine PCV immunization of children in the EPI in South Africa. The study included 82 HIV-infected, 40 HEU and 244 HIV-unexposed children (67). Chest X-rays were reported according to the proposed WHO standardized chest X-ray interpretation for pneumonia (15). Jeena *et al* found a prevalence of CXR-PEP in 55% HIV-infected, 40% HEU and 35% HIV-unexposed children. CXR-PEP was twice as common in HIV-infected compared with HIV-unexposed children (OR 2.3; 95% CI 1.3-4.0). There was no significant difference between HEU

and HIV-unexposed children for CXR-PEP. Conversely other infiltrate was prevalent in 45% HIV-infected, 58% HEU and 65% HIV-unexposed children, with 60% lower prevalence of other infiltrate in HIV-infected compared to HIV-unexposed children (OR 0.4; 95% CI 0.3-0.8); and no significant difference between HEU compared with HIV-unexposed children (67).

Evaluation of the utility of chest X-rays for predicting treatment failure (defined in the study as being failure to respond to empirically prescribed therapy by 48 hours, or worsening of respiratory status at any point in the 14 day study period), indicated that HIV-infected children who failed therapy were more likely to have other infiltrate (41%) than CXR-PEP (11%) (OR 5.5; 95% CI 1.6-21.4). In contrast, among the HEU group, children who failed treatment were more likely to CXR-PEP (31%) than other infiltrates (13%), (OR 4.13; 95% CI 0.9-20.6). Limitations of this study included a small number of HEU children (n=40) and lack of microbiological testing for etiological agents (67).

2.5 Critical Literature Review of Chest X-ray Pattern Association with Acute Phase Reactants and Clinical Signs in Childhood Community Acquired Pneumonia

2.5.1 Literature Demonstrating an Association between Acute Phase Reactants, Clinical and Chest X-ray Patterns in Childhood Pneumonia

Many studies in children found that an elevated C-reactive protein (CRP) is a good predictor of chest X-ray confirmed pneumonia ie: high CRP >40 mg/dL is associated with air space consolidation (63, 65, 68, 69) where-as a low CRP is associated with interstitial infiltrate (63, 69). Furthermore Don *et al* found other inflammatory markers like erythrocyte sedimentation rate (ESR), procalcitonin (PCT) and high total white cell count (WCC), to be elevated in

childhood pneumonia cases with air space/alveolar consolidation compared to those with only interstitial infiltrates, refer to Table 2.4 (63).

2.5.1.1 Clinical Signs: Crackles, Fever, Hypoxia and Tachypnea

Studies found that crackles was associated with chest X-ray pneumonia (70-72), but with a low sensitivity (43%-73%), and specificity (48%-73%) (71, 72). Ayalon *et al* found that hypoxia was associated with air space consolidation (OR 2.4; 95% CI 1.0-5.6), but did not evaluate the sensitivity and specificity of hypoxia in predicting chest X-ray changes in childhood CAP (70).

Other literature found that fever predicts chest X-ray pneumonia (70, 71, 73-75) with a good sensitivity (72%-99%), but low specificity (20%-37%) (71, 73, 75). Refer Table 2.3. Zukin *et al* found the clinical sign with the highest sensitivity with chest X-ray air space disease was fever (sensitivity of 94%), with a negative predictive value of 97%, but the specificity was low 36% (73). They found that combining multiple clinical signs suggestive of pneumonia increased the predictive yield for chest X-ray pneumonia (73, 76). Similarly Lynch *et al* found that combining fever with other clinical signs of pneumonia increased the sensitivity of chest X-ray air space disease from 93% to 96% (71, 76).

Studies have found that tachypnea was a good predictor of pneumonia on chest X-ray in children with childhood CAP (71-74, 77, 78). The sensitivity of tachypnea ranged from 13%-74%; with better specificity (between 67%-95%) (71-73, 78); refer Table 2.3.

2.5.2 Literature Demonstrating No Association between Acute Phase Reactants, Clinical and Chest X-ray Changes in Childhood Pneumonia

Contradictory literature has found no association between certain clinical, immunological parameters and chest X-ray findings in children. Numerous studies found no association between

tachypnea (61, 75, 79, 80), hypoxia (75, 80, 81) and fever (61, 75, 80) in predicting chest X-ray findings in children presenting with CAP; refer Table 2.3.

A recent meta-analysis of 18 articles to identify clinical symptoms and signs predictive of chest X-ray confirmed pneumonia in children less than 5 years found that no single clinical feature was sufficient to diagnose chest X-ray confirmed pneumonia. The clinical feature with the highest likelihood ratio was tachypnea (respiratory rate greater than 50 breaths per minute); (OR 1.90; 95% CI 1.45-2.48), but the pooled sensitivity and specificity from 6 studies was low (62%, 95% CI 0.26-0.89) and (59%, 95% CI 0.29-0.84) respectively (82). The authors recommended combining clinical symptoms and signs in the management of children under 5 years with WHO clinical criteria of pneumonia (82).

2.5.3 Extent of Radiographic Pneumonia and Disease Severity

McClain *et al*, investigating 406 children <18 years, median age 3 years (IQR 1-6 years), who were all hospitalized for pneumonia in four hospitals in the USA, found that unilateral and bilateral consolidation was associated with intensive care unit admission. Children with bilateral air space consolidation had higher odds for supplemental oxygen use (OR 2.7; 95% CI 1.2-5.8); and invasive mechanical ventilation (OR 3.0; 95% CI 1.2-7.9) compared to those with less extensive lung changes on chest X-ray. They concluded that children with multi lobar air space consolidation and large pleural effusions had greater clinical disease severity (83). Grafakou *et al* investigating 167 children 1 to 14 years, with a median age 4.5 years that were hospitalized for fever, found that the location and the size of air space consolidation on chest X-ray were useful predictors of severity of pneumonia. The mean duration of fever and hospitalization was significantly higher in children with left-sided chest X-ray air space consolidation (84). The lack of standardized reporting in the definition of "chest X-ray pneumonia" in the different described

studies is important, refer Table 2.3. A number of these studies did not differentiate in their methodology between air space/alveolar pattern and interstitial infiltrate on chest X-ray (71, 73, 77-81). Hence direct comparisons between these studies need to be interpreted with caution.

2.6 Critical Literature Review of Chest X-ray Pattern Association with Microbiological Etiology in Childhood Community Acquired Pneumonia

A Pubmed search was conducted for English language articles published from 1970 to 2016, in order to determine the breadth of existing literature relating to patterns of chest X-ray changes in childhood pneumonia, and their association with pathogens implicated in pneumonia causation. The keywords used in the search included: “chest X-ray” and “chest radiograph” and “children” and “paediatric” and “pneumonia” and “community acquired pneumonia” and “hospitalized” and “microbiological etiology” and “putative agent” and “bacteria” and “respiratory virus”. The titles and abstracts of articles were perused and the full manuscript of eligible research articles, were reviewed. Studies that used nasopharyngeal (NP) secretions for bacterial identification as the reference standard (85-87) were not considered in this literature review, due to the poor predictive value of NP swabs for attributing pneumonia etiology causality (88). The review of selected studies were collated and tabulated according to country of origin, publication date, authorship, population characteristics including immunization status with Hib and PCV, microbes investigated, association between chest X-ray patterns and microbiological etiology and main conclusions from the studies, refer Table 2.4. Eight studies were considered appropriate for inclusion in Table 2.4.

Literature from the 1970s and 1980s proposed that chest X-rays could be useful in differentiating between bacterial and respiratory viral associated pneumonia, with lobar consolidation being associated with bacterial infection and interstitial reticulo-nodular infiltrate being associated with respiratory viral infection (89, 90). These studies were based on clinical signs and

symptoms without the support of microbiological diagnoses (89, 90). During the 1980s studies comparing chest X-ray findings to specific putative etiologic agents, diagnosed predominantly based on respiratory viral serology, viral culture and urinary antigen analysis and blood culture for bacteria failed to establish any association between chest X-ray findings and the putative pathogens (91-93). However the suboptimal sensitivity of identifying bacteria through blood culture was a limitation in the interpretation of these findings.

In the 1990s investigational approaches including paired serological assays for the detection of immune responses to respiratory viruses and common bacterial infections were developed (64). The results from selected studies assessing the association of chest X-rays features in relation to some of these investigational and other traditional diagnostic assays are summarized in Table 1.4. Korppi *et al* investigated for 8 possible pathogens in 61 children (69) and Virkki *et al* investigated 17 pathogens in 254 children (65). Both studies found a significant association between air space/alveolar consolidation and bacterial infection and interstitial infiltrate and respiratory viral or mixed bacterial-viral infection (65, 69). These findings were however in contrast to those of other investigators including Don *et al* (63), Cevey-Macherel *et al* (94), Wahlgren *et al* (64) and Esposito *et al* (68) who failed to establish a statistically significant association between chest X-ray and putative microbiological etiology (63, 64, 68, 94); refer Table 2.4 for details of these studies.

These studies were limited by small cohort size (63, 68, 69, 94), limited number of microbes investigated (63, 64, 68, 69), the inclusion of both ambulatory and hospitalized children in certain studies (63, 64), reporting of chest X-rays by a single radiologist (62, 68, 94), lack of a global ‘gold standard’ for microbe-specific diagnosis of bacteria and the heterogeneity of microbiological methods used. Nascimiento-Carvalho *et al* who investigated 1456 children with

chest X-ray confirmed pneumonia (air space/alveolar versus interstitial infiltrates) and blood culture found no correlation between radiological findings and blood culture results (95). However, similar to the study by Madhi *et al* (62) a major limitation of this study was the low sensitivity of blood culture (2–3%) (95).

Vuori-Holopainen *et al* who investigated microbiology using a direct method ie: lung aspiration and polymerase chain reaction (PCR) found that 80% of the air space/alveolar consolidation was due *S. pneumoniae*, 10% due to atypical bacteria and 5% due to respiratory viral infection (96), (refer to Table 2.4). A literature review of 59 studies by Vuori-Holopainen *et al*, in which lung aspiration was performed on air space consolidated lung, where testing for respiratory viruses were rarely done, identified bacteria in 66% of cases in Europe, 32% in North America, 44% in South America, 66% in Africa and 51% in Asia (97). Limitations of some of these studies include small sample size, limited number of pathogens investigated and combined analyses of bacterial pathogens (96, 97). However these direct lung aspiration studies support the findings by Korppi *et al* (69) and Virkki *et al* (65), Table 2.4, that air space/alveolar consolidation is predominantly associated with bacterial infection.

To date; a clinically acceptable gold standard for the diagnosis of bacterial pneumonia has not yet been developed. The ideal gold standard for the diagnosis of bacterial pneumonia should be accurate, minimally invasive and readily available (98).

Table 2.2 Review of Selected Studies on Chest X-ray Findings in Hospitalized Children with Community Acquired Pneumonia

Study	Population Characteristics	Prevalence of Chest X-Ray Findings	Distribution Patterns on Chest X-ray	Chest X-ray Pattern Stratified by Age	Other Findings
Key *et al.* 2011(59) (Brazil) Study period 03/2006 -02/2008	N=301 Age: 12 Days –59months Median Age 17 Months No immunization with PCV	-Alveolar infiltrate 40% -Interstitial infiltrate 54% CXR with abnormalities -Alveolar-interstitial 13% -Hyperinflation 23% -Atelectasis 36% -Peri-bronchial thickening 31% -Pleural effusion 23% -Pulmonary abscess 2%	Lobar consolidation Right 68% Upper lobe 32% Both lobes 4%	-Hyperinflation more common in infants 28% vs 4% (*P*<0.001)	-Upper lobe involvement predicted severity in 65% (95% CI 41–84%) in children 1-5 years
Ferrero *et al.* 2010 (60) (Argentina, Brazil and Dominican Republic) Study period unknown	N=2536 Age: 3–59 Months Median Age: unknown No Immunization with PCV	-Alveolar infiltrate 75% -Pleural effusion 16% -Interstitial infiltrate 9% -Atelectasis 6% -Pneumatocele 0.9% -Abscess 0.6% -Pneumothorax 0.4%	Lobar consolidation Unilateral 79% Bilateral 21% Right 76% Unilobar 70% Lower lobe 54%	-Interstitial infiltrate more common < 1 year (*P* <0.001)	-Pneumococcal isolation 11.2% in those with upper lobe involvement OR 1.8 (95% CI 1.3–2.7) -Pneumococcal bacteraemia in those with upper lobe involvement OR 1.7 (95% CI 1.2–2.6)
Barti *et al.* 2008 (61) (India) Study period 05/1997-06/1998	N=83 Age: 3 Months - 7.3 Years Median Age 1.25 Years No Immunization with Hib or PCV	-Lobar consolidation 52% -Interstitial infiltrate 31% -Hilar lymphadenopathy 24% -Hyperinflation1%	Lobar consolidation Right 61% Left 21% Bilateral 19% Interstitial infiltrate Bilateral 69% Right 23%	-Normal CXR more common in infants compared to children >1 year 26% vs 9% (*P*=0.07)	-No statistical association between CXR findings and clinical outcomes: fever, tachypnea, duration of hospitalization
Madhi *et al.* 2002(62) (South Africa) Study period 03/1997-02/1998	N=1186 Age: 2-60 Months Median Age 8 Month No Immunization with PCV or HiB, no ART	CXR pattern — HIV-infected — HIV-uninfected Alveolar consolidation — 64% — 42% Bronchopneumonia — 29% — 38% Pleural effusion — 11% — 9% Cavitation — 2% — 1% Hilar lymphadenopathy — 26% — 23% Hyperinflation — 42% — 41%		HIV-infected older than uninfected and more likely to have bacteraemia (OR 1.8; CI 95% 1.1-2.9), less likely to have a respiratory virus isolated (OR 0.3; CI 95% 0.2- 0.5)	-Alveolar consolidation was more common in HIV-infected than HIV-uninfected (*P*<0.001) -Bronchopneumonia and normal CXR more common in HIV-uninfected compared to HIV-infected (*P* = 0.001) and (*P*<0.001) respectively

Table 2.3 Review of Selected Studies of Chest X-Ray Pattern Association with Clinical Parameters in Childhood Community Acquired Pneumonia

Study	Population Characteristics	Chest X-ray Definitions Used	Clinical Parameters associated with Chest X-Ray Patterns	Clinical Parameters Not associated with Chest X-Ray Patterns
Leventhal *et al.* (77) (USA) 1982	N=136 Age: 3 months-15 years	Positive infiltrate	Tachypnea	N/S
Zukin *et al.* (73) (USA) 1986	N=125 Age: ≤17 years	Chest X-ray pneumonia Major abnormality: atelectasis, pleural effusion Normal chest X-ray	Fever Tachypnea	N/S
Dai *et al*. (72) (China) 1995	N=54 Age: <5 years	Chest X-ray pneumonia Bronchitis	Tachypnea Crackles	N/S
Palafox *et al.* (78) (Mexico) 2000	N=110 Age: 3 days -5 years	Chest X-ray pneumonia: micronodular or macronodular infiltrations or condensations in the lung	Tachypnea	Chest in drawing Alveolar Rales
Rothrock *et al.* (79) (USA) 2001	N=329 Age: ≤5 years	Chest X-ray pneumonia: pneumonia or an infiltrate	N/S	Tachypnea
Tanen *et al.* (81) (USA) 2002	N=762 Age: < 24 months	Chest X-ray pneumonia: opacity on chest X-ray	N/S	Hypoxia
Lynch *et al.* (71) (Canada) 2004	N=570 Age: 1-16 years	Chest X-ray positive: pulmonary opacities present Chest X-ray negative: no pulmonary opacities	Fever Tachypnea Crackles	N/S
Renault *et al.* (74) (Canada) 2004	N=88 Age: not defined	Chest X-ray pneumonia: segmental or lobar consolidation	Fever Tachypnea	N/S
Barti *et al*. (61) (India) 2008	N=83 Age: 3 months-7.3 years	Lobar consolidation Interstitial infiltrate	N/S	Fever Tachypnea Length of hospitalization
Wingerter *et al*. (80) (USA) 2012	N=324 Age: ≤5 years	Chest X-ray pneumonia: consolidation or infiltrate or radiographic pneumonia	N/S	Fever Hypoxia Tachypnea
Zimmerman *et al.* (75) (Israel) 2012	N=278 Age: 2 months-18 years	Lobar or air space consolidation Interstitial or broncho-alveolar or peribronchial infiltrate	Fever	Tachypnea Hypoxia
Ayalon *et al.* (70) (Israel) 2013	N=525 Age: 1 month-16 years	Air space consolidation: lobar or segmental Reticular nodular infiltrate: bronchopneumonia	Fever Hypoxia Crackles	N/S

Table 2.3 Review of Selected Studies of Chest X-Ray Pattern Association with Clinical Parameters in Childhood Community Acquired Pneumonia continued

Study	Sensitivity, Specificity, PPV*, NPV^ of **Fever** in predicting CXR	Sensitivity, Specificity, PPV*, NPV^ of **Tachypnea** in predicting CXR	Sensitivity, Specificity, PPV*, NPV^ of **Crackles** in predicting CXR	Sensitivity, Specificity, PPV*, NPV^ of **Hypoxia** in predicting CXR	**Other Findings**
Leventhal *et al.* (77) (USA) 1982	N/S	N/S	N/S	N/S	Cough- positive infiltrate 21% Tachypnea- positive infiltrate 32%
Zukin *et al.* (73) (USA) 1986	77%, 37%, 47%, 69%	54%, 80%, 65%, 70%	32%, 71%, 61%, 43%	N/S	N/S
Dai *et al*. (72) (China) 1995	N/S	50%, 71%	62%, 48%	9%, 94%	Tachypnea- CXR pneumonia 32% Crackles- CXR pneumonia 39% Hypoxia- CXR pneumonia 6%
Palafox *et al.* (78) (Mexico) 2000	N/S	74%, 67%, 69%	46%, 79%, 68%	N/S	N/S
Rothrock *et al.* (79) (USA) 2001	N/S	10%, 5%, 3%, 19%	23%, 15%, 7%, 43%	N/S	N/S
Tanen *et al.* (81) (USA) 2002	N/S	N/S	N/S	N/S	45% of children with CXR pneumonia had O2 sats $\geq$ 98%
Lynch *et al.* (71) (Canada) 2004	92%, 20%, 82%, 39%	13%, 95%, 66%, 60%	43%, 73%, 70%, 47%	N/S	fever- OR 3.1 (95% CI 1.7-5.3) tachypnea- OR 1.2 (95% CI 0.2-1.9) crackles- OR 2.0 (95% CI 1.4-2.9)
Wingerter *et al*. (80) (USA) 2012	35%, 73%, 24%, 82%	39%, 70%, 24%, 82%	N/S	67%, 44%, 32%, 77%	Fever- CXR pneumonia 24% Hypoxia- CXR pneumonia 32%
Zimmerman *et al.* (75) (Israel) 2012	99%, no specificity 38%, 95%	N/S	N/S	N/S	Fever- OR 13.9 (95% CI 1.8-109) Wheezing - OR 0.6 (95% CI 0.3-0.9)
Ayalon *et al.* (70) (Israel) 2013	N/S	N/S	N/S	N/S	Fever- OR 2.1 (95% CI 1.2-2.1) Hypoxia- OR 2.4 (95% CI 1.0-5.6) Crackles- OR 2.2 (95% CI 1.3-3.7)

* positive predictive value

^ negative predictive value

N/S: not specified

Table 2.4 Review of Selected Studies of Chest X-ray Pattern Association with Microbiological Etiology in Childhood Community Acquired Pneumonia

Study	Population Characteristics	Microbes Investigated and Findings	Association between CXR patterns and etiology	Conclusion
Don *et al.* 2009 (63) (Italy) Study period 10/2001 -12/2002	N=68 Median age 3.6 years Hospitalized and ambulatory with CAP	**14 microbes** using paired serological assays, virus NP swab investigated with microimmunofluorescence Causative agent 65% cases 69% bacterial infection 62% viral infection 31% mixed viral – bacterial	**CXR pattern** / ***Strep Pneum*** / **Atypical Bacteria** / **Viral** Alveolar <5years: 39% / 25% / 33% Alveolar≥5 years: 11% / 39% / 9% Interstitial<5 years: 22% / 21% / 52% Interstitial≥5 years: 28% / 14% / 5%	-No significant association between radiology and etiology (p=0.08), using a frequentist statistical approach. -Alveolar infiltrate associated with higher inflammatory markers compared with interstitial infiltrates
Cevey-Macherel *et al.* 2009 (94) (Switzerland) Study period 03/2003-12/2005	N=99 Age:2months-5 years Median age 29 months Hospitalized with CAP No immunization with PCV	**17 microbes** PCR for 13 viruses and atypical bacteria Bacterial infection identified by paired serological assays with immunofluorescence Causative agent 86% cases 53% bacterial infection 45% *Streptococcus pneumoniae* 67% viral infection 33% mixed viral- bacteria	**CXR** / **Bacteria** / **Virus** / **Mixed** Alveolar consolid: 16% / 25% / 26%	-Used **WHO CXR reporting** -No significant association between radiology and etiology (p=0.911), using a frequentist statistical approach -High prevalence of viruses and frequent co-infection in CAP
Wahlgren *et al.* 2005 (64) (Sweden) Study period 1982-1985	N=346 Age: 0-15 years Hospitalized and ambulatory with CAP	**12 microbes** using paired serological tests for virus, bacteria, virus culture on NP Causative agent 75% cases 21% bacterial infection 32% viral infection 19% mixed infection 2% *Mycoplasma pneumoniae*	**CXR pattern** / **Bact** / **Virus** / **Mixed** Alveolar <2 yrs: 15% / 35% / 31% Interstitial < 2yrs: 11% / 40% / 21% Mixed <2 yrs: 11% / 32% / 14% Alveolar 2-5 yrs: 25% / 39% / 15% Interstitial 2-5 yrs: 22% / 29% / 20% Mixed 2-5 yrs: 10% / 38% / 14%	-No significant association between radiology (alveolar infiltrate or interstitial infiltrate) and etiology using a logistic regression model -Higher frequency of viral infection in younger children and bacterial infection in older children
Madhi *et al.* 2002 (62) (South Africa) Study period 03/1997-02/1998	N=1186 Age: 2-60 months Median age 8 month Hospitalized with CAP No immunization with PCV or HiB No ART	**7 viruses** from NP swabs using immunofluroscein assays and culture, bacteria using blood culture 61% investigated for both bacteria and viruses 3.1-4.7% bacteria blood culture yield	**CXR pattern** / **Bact Pneum** / ***Strep pneum*** / **Viral** Alveolar consolid HIV- infected: 79% / 77% / 56% Alveolar consolid HIV-uninfected: 65% / 83% / 36%	-Viral infection more likely to present with alveolar consolidation in HIV-infected compared to HIV-uninfected (P=0.02)

Esposito *et al.* 2002 (68) (Italy) Study period unknown	N=196 Age: 2-5 years Median age 3.7years Hospitalized with CAP	**3 microbes** using paired serological assays, NP swab PCR for Atypical bacteria <u>Causative agent 66% cases</u> 25% *Streptococcus pneumoniae* <u>*Atypical bacteria*</u> 15% *Mycoplasma pneumoniae* 3% *Chlamydophila pneumoniae*	**CXR pattern** / ***Strep pneum*** / **Atypical Bacteria** / **Mixed** Alveolar consolid 15% 9% 13% Lobar alveolar 38% 26% 31% Reticulo-nodular 27% 46% 31% Peri-hilar opacities 31% 44% 56% Peribronchial thick 6% 9% 5% Hyperinflation 10% 13% 13% Pleural fluid 6% 7% 6%	-No clinical, laboratory or radiographic patterns correlated with the different etiologic diagnoses using a frequentist statistical approach -CRP higher in pneumococcal infections
Virkki (65) *et al.* 2002 (Finland) Study period 01/1993 -12/1995	N=254 Age: 0.1 -16.7 years Median age 3.8 years Hospitalized with CAP	**17 microbes**, bacteria using paired serological assays, virus NP swab with enzyme immunoassay, viral culture, PCR for rhinovirus <u>Causative agent 85% cases</u> 62% viral infection, 53% bacterial infection 30% mixed viral-bacterial 37% *Streptococcus pneumoniae* 29% respiratory syncytial virus	**CXR pattern** / **Bacterial** / **Viral** Alveolar 72% 49% Lobar alveolar 36% 15% Interstitial 28% 49% Hyperinflation 35% 44% Atelectasis 7% 11% Lymph nodes 10% 14% Pleural fluid 6% 5%	-Alveolar infiltrate, especially lobar infiltrate associated with bacterial infection 72% vs 49%, (p= 0.001) and Interstitial infiltrate only more common in respiratory viral infection compared to bacterial infection 49% vs 28%, (p= 0.001), using a frequentist statistical approach - Increased CRP predicted bacterial pneumonia
Vuori-Holopainen *et al*. 2002 (96) (Finland) Study period 12/1997-12/2000	N=34 Age:0.8-14 years Median age:2.9 years Hospitalized with CAP No immunization with PCV or Hib	**6 microbes** investigated <u>Causative agent 59% cases</u> Lung aspiration of consolidated lung, PCR used for *Streptococcus pneumoniae, H. infulenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae,* enterovirus, rhinovirus. Viral culture and antigen detection	**CXR pattern** / ***Strep pneum*** / **Atypical Bacteria** / **Viral PCR** / **Viral Culture** Alveolar consolid 80% 10% 5% 5%	-Alveolar consolidation associated with *streptococcus pneumonia* -56% of patients had lower lobe and 6% bilateral lung air space consolidation -Selection bias due to selection of patients with peripheral dense air space consolidation -Blood culture bacterial yield 10%
Korppi *et al.* 1993 (69) (Finland) Study period 1981-1982	N=61 Age: 0-5 years Hospitalized with CAP No immunization with PCV or Hib	**8 microbes** using paired serological assays for bacteria, NP swab assays for virus <u>Causative agent 100% cases</u> 67% bacterial infection 44% *Streptococcus pneumoniae* 67% viral infection 56% respiratory syncytial virus	**CXR** / **Bacteria** / ***Strep pneum*** / **Virus** / **Mixed** Alveolar infiltrate 60% 48% 35% 38% Interstitial infiltrate 40% 52% 65% 62%	- Alveolar infiltrate associated with isolated bacterial infection and Interstitial infiltrate associated with viral infection or mixed infection using a frequentist statistical approach ($p < 0.05$)

2.6.1 Chest X-ray Findings in Children with Pulmonary TB

The diagnosis of pulmonary TB (PTB) is difficult in children due to non-specific clinical signs and limited utility of the tuberculin skin test in HIV-infected children (37, 99). Sputum smear microscopy from gastric washings and induced sputa have a low yield (4% to 7%) (100), with TB culture producing better, but low yields of approximately 7% to 30% (101-104). Due to the difficulty in obtaining microbiological confirmation of PTB in children, diagnosis often relies on a combination of clinical and radiological findings (102, 105). Chest X-rays are the standard imaging modality of choice in countries like South Africa for the diagnoses of PTB in children, due to the high HIV and TB disease burden and limitations in resources like CT in primary and secondary public sector hospitals (36, 37, 99, 106).

The radiologic hallmark of primary childhood TB is hilar and/or mediastinal lymphadenopathy (105, 107, 108) and this may be the only radiographic finding prevalent in 46%-50% of cases of early primary childhood PTB (107, 109) . However an important limitation of reporting intrathoracic lymphadenopathy on chest X-rays in children, is the poor inter-reader agreement, as described in the current literature (37, 99, 102, 110). Other radiographic patterns associated with PTB are miliary infiltrate (33%) or pulmonary cavitation (12%) (102, 109). Lung parenchymal involvement is a non-specific finding in primary PTB and commonly appears as an area of air space disease in a segmental or lobar distribution prevalent in 44% of infants and children with clinically-diagnosed PTB, while pleural effusions (8%) are uncommon in primary TB in infants and young children (99, 109).

Milkovic *et al* investigating the chest X-ray findings in 172 children with primary PTB found that lymphadenopathy (84%) was the most common finding, significantly more common in children 0-4 years. This was followed by parenchymal changes 61% (111). These results are

similar to those of Kim *et al* investigating 41 children with CT chest who found that lymphadenopathy (83%) was the most common finding, followed by air space consolidation (49%), then miliary infiltrate (17%) (112). Schaaf *et al* investigated 596 children, median age 31 months with culture -confirmed PTB, where 281 (47.1%) were HIV-uninfected, 133 (22.3%) HIV-infected and 182 (30.5%) not tested for HIV. HIV-infected children had a two-fold greater odds for air space/alveolar opacification (OR 1.9; 95% CI 1.1–3.2) and cavitation (OR 2.28, 95% CI 1.4–3.6) compared with HIV-uninfected children (113). This was in contrast to the findings of Srinakarin *et al* who found no significant difference between HIV-infected compared with HIV-uninfected children: interstitial infiltrate (75% vs. 73%), intrathoracic lymphadenopathy (33% vs. 32%), air space/alveolar consolidation and miliary infiltrate (114). To our knowledge the chest X-ray finding in HEU children with culture confirmed or clinically-diagnosed PTB has not been described in the literature to date.

2.6.2 Chest X-ray Findings in *Pneumocystis jiroveci* Pneumonia

Pneumocystis jiroveci pneumonia is a common cause of morbidity and mortality in HIV-infected infants in sub-Saharan Africa (99). Prior to recommendations for the use of trimethoprim-sulphamethoxazole prophylaxis and widespread national ART guidelines in children, *Pneumocystis jiroveci* was the common opportunistic infection in HIV-infected infants (37, 99). In a review of 7 studies with 11 children diagnosed with PJP, the common findings were homogenous opacification prevalent in 45% of children, cysts prevalent in 27% and pneumothorax prevalent in 36% (109). To our knowledge the chest X-ray findings in HEU children with PJP have not been described to date.

2.6.3 Chest X-ray Findings in HIV-infected Children in a Chronic Setting

Du Plessis *et al* investigated chest X-ray abnormalities in 92 HIV-infected children initiating ART at an outpatient department in Kwa-Zulu Natal, found a 46% prevalence of chest X-ray abnormalities, with a high prevalence of air space disease (28%), cardiomegaly (21%) and radiological TB (9%) (115). This was similar to findings by Kouakoussui *et al* (Ivory Coast) with an overall prevalence of 51% for any chest X-ray abnormality, including air space disease (22%) and interstitial disease (17%) (116). Another study from Cape Town by Pitcher *et al* who investigated 303 HIV-infected children enrolled on an isoniazid prophylaxis study who had no "acute respiratory symptoms", and where 77% were not on ART, found that 84% had abnormal chest X-rays, 51% had grade 2 changes i.e: pulmonary opacification (28%), reticulo-nodular infiltrate and opacification (12%) and reticulo-nodular infiltrate only (11%) and 33% had grade 1 changes ie: bronchial thickening. The distribution of grade 2 changes was multifocal or diffuse in 75% of cases (14). Both South African studies were limited by the reporting of chest X-rays by a single radiologist which may lead to observational bias (14, 115). However the strength of the study by Pitcher *et al* using modified WHO standardized chest X-ray interpretation criteria (15), was that the chest X-rays were reported by a paediatric radiologist with more than twenty years of clinical experience and inter-observer variability is less on "overt grade 2" chest X-ray findings (14).

HIV-infected children have an increased risk of developing chronic respiratory disease. Risk factors include the "frequency and severity" of acute chest infections, aspiration pneumonia, increased risk for PTB, cardiovascular disease and lymphocytic interstitial pneumonitis (LIP) (109). Pitcher *et al* investigating 258 HIV-infected children in Cape Town, South Africa found a cumulative incidence of severe, persistent severe chest X-ray changes in 60%, median duration 18 months (104). Persistent homogenous opacification occurred in 21% of all children. Of the 73

children diagnosed with PTB (clinical TB 91% and culture-confirmed TB 8%) opacification with nodules was prevalent in 40%, nodules only was prevalent in 19%, bronchiectasis with other abnormalities was prevalent in 12% and bronchiectasis only was prevalent in 1%. Severity of chest X-ray change was associated with previous chest X-ray severity (OR 120.8; 95% CI 68.7-212.3), hospitalization for a previous chest infection in the past 6 months (OR 1.9; 95% CI 1.1-3.3), lack of ART (OR 1.7; 95% CI 1.3-2.3), and young age (<18 months) at enrolment (OR 1.4; 95% CI 1.1-1.8) (104).

Nortan *et a*l investigating 86 HIV-infected children in the USA found a cumulative incidence of 33% of chronic lung changes (defined as focal or diffuse parenchymal consolidation or nodular disease that lasted more than 3 months, or increased broncho-vascular markings or reticular densities that lasted more than 6 months) on chest X-ray at 48 months of age, with a median age of onset of 18 months. Pulmonary TB was reported in only (2%) of children, presenting with nodular densities on chest X-ray (117). Sheik *et al* also from USA reported a prevalence of bronchiectasis of 16% in HIV-infected children; (median age 7.5 years and ART status unknown). The association with bronchiectasis that was found to be most common was with LIP (34%), followed by unresolved pneumonia (28%) and recurrent pneumonia (13%) (118).

2.6.4 Chest X-ray Association with Immune-suppression in HIV-Infected Children

Du Plessis *et al* described a 54% (95 % CI 12%-76%) reduction in risk of airspace disease on chest X-ray in children who accessed ART compared to those not on ART. Children with immune suppression were 50% less likely to have air space disease (115). This is in contrast to Pitcher *at al* who found that children with advanced clinical HIV disease (OR 6.9; 95% CI: 1.0-25.6) and CD4 counts <20% (OR 1.8; 95% CI: 1.0–3.0) were more likely to have grade 2 chest X-ray abnormalities (14). Consistently Sheik *at al* also found that the development of

bronchiectasis was associated with the severity of immune suppression in HIV-infected children, with all who had bronchiectasis having CD4 counts of < 100 cells/mm^3 (118). Nortan *et al* found that HIV-infected children with significantly lower mean CD4 counts and higher viral loads had an increased incidence of chronic chest X-ray changes. However, on follow up these changes resolved over time in many children with significantly lower CD4 counts without associated clinical improvement. This may be due to decreased ability to mount an immune response and manifest chest X-ray changes in severely immune suppressed children (117).

2.7 Computer Aided Diagnosis for WHO Standardized Chest X-ray Interpretation for Pneumonia Epidemiological studies and Vaccine Efficacy Trials in Children

2.7.1 Limitations of WHO Standardized Chest X-rays Interpretation for Vaccine Efficacy Trials and Pneumonia Epidemiological studies in Children

Studies using the WHO standardized chest X-ray interpretation definitions demonstrated fair to moderate agreement (*Kappa*=0.40-0.58) for any diagnosis (18, 119, 120), moderate to substantial agreement (*Kappa*=0.48-0.62) for end-point consolidation, fair to substantial agreement (*Kappa*=0.27-0.66) for other infiltrate (119-121) and moderate agreement (*Kappa*=0.58) for pleural effusion (120). Overall the literature demonstrates that the inter-reader agreement for CXR-PEP is better compared to inter reader agreement for other infiltrate (119-121).

Madhi *et al* estimated in a post hoc analysis that using the CXR-PEP for evaluating PCV efficacy against pneumococcal pneumonia, underestimated the vaccine preventable burden of pneumonia of the PCV-9 vaccine by 63% (122). This may be attributed to the pre-determined WHO chest X-ray endpoint being geared toward high specificity, rather than high sensitivity (15, 123). This was further corroborated with a study in the USA, where since the introduction of childhood

PCV immunization, there has been a 36% reduction in all-cause pneumonia, many of which were likely not to have fulfilled the WHO predetermined endpoint of chest X-ray confirmed pneumonia (123, 124). Madhi *et al* proposed that the inclusion of other infiltrate with a raised CRP $\geq$ 40mg/L as an end-point when evaluating PCV efficacy may assist in capturing bacterial pneumonia cases without evidence of CXR-PEP (122). However a recent study evaluating effectiveness of PCV against hospitalization with presumed bacterial pneumonia (PBP) in HIV-uninfected South African children, where either of 2 end-points were used: CXR-PEP or other infiltrate with CRP ≥40 mg/L found that the vaccine efficacy (VE) were similar (VE=20.1% ; 95% CI -9.3% -41.6% in children aged ≥8 weeks and (VE=39.2% ; 95% CI 8.46% -59.6%) to that measured by the earlier randomised PCV-9 trial using different vaccination schedules and CXR-PEP as the only end-point (125).

Limitations of the WHO standardized interpretation of chest X-Rays were discussed at the Hib Initiative Radiology Workshop in Hanoi, Vietnam in 2011 (120) and at the WHO Short and Long-term PCV Impact Evaluation meeting in Geneva, Switzerland in 2013 (126). There has also been "significant drift" in the application and maintenance of WHO standards, despite the use of a WHO training module (120). In the past the WHO Radiology Working Group provided support for vaccine and epidemiological studies, with chest X-ray arbitration for discordant films and reading of a random selection of positive and negative chest X-rays for quality control. However due to financial constraints and the lack of technical capacity within WHO, the organization was no longer able to offer this support up until 2015 (120).

2.7.2 WHO Chest Radiography in Epidemiological Studies (CRES) project

The new WHO Radiology Working group reconvened as the WHO Chest Radiography in Epidemiological Studies (CRES) committee in December 2015. The WHO CRES project is a

sub-study to the PCV Technical Co-ordination project, based at the Murdoch Children's Institute in Melbourne Australia, in collaboration with Johns Hopkins Bloomberg School of Public Health, Baltimore, USA and the Immunizations, Vaccines and Biologics Department of WHO, Geneva, Switzerland. Prof Madhi and Dr N Mahomed are members of the WHO CRES committee, with Dr Mahomed also representing the World Federation of Paediatric Imaging (WFPI) on this committee.

The WHO CRES committee meeting took place on 23-24 June 2016 at the London School of Hygiene and Tropical Medicine. The current aim of the WHO CRES project is to provide certain clarifications to the original definitions, aimed at maintaining specificity of chest X-rays as an end-point in pneumonia epidemiological and vaccine efficacy studies in children and "producing reproducible chest X-ray readings for future studies". A new set of open source training chest X-rays are being developed under the WHO CRES project. The WHO CRES project also integrates chest X-ray quality optimization guidelines and site safety assessments.

Addressing some of the these limitations in low and middle income countries, including the limited number of radiologists where clinicians often interpret chest X-rays (14, 48), and the limited number of radiologists and paediatricians with expertise in WHO standardized chest X-ray interpretation, machine based techniques like computer aided diagnosis (CAD) may play an important future role and has been proposed at the WHO CRES meeting.

2.7.3 Critical Literature Review of Computer-Aided Diagnosis of Chest X-rays

The application of CAD in chest X-rays typically comprises of four phases: lung field segmentation, lung field subdivision, feature extraction and classification (127). Multiple regions of interest (ROI) are manually or automatically selected within the lung fields. Features, in the form of textural measurements are extracted from the ROI and classified using rule-based and/or

pattern recognition techniques resulting in probability maps for each of the regions in the lung fields. Combined results are used for an overall diagnosis for each chest X-ray eg: normal or interstitial abnormality (127).

Automatic and accurate lung field segmentation is an essential step for developing an automated CAD for chest X-rays. Lung field segmentation remains a challenge in the application of CAD for chest X-rays due to superimposed anatomical structures including ribs, scapulae, vertebral bodies, clavicles and pulmonary vasculature (127, 128).

Most of the research on CAD in chest X-rays have concentrated on the detection of pulmonary nodules (benign or malignant) but recently the interest in classification of abnormal chest X-rays using CAD has grown (129). Van Ginneken *et al* initiated the first study on the use of CAD on PTB diagnosis on adult chest X-rays (130). Their method involved lung field segmentation using the automatic active shape model (ASM) with subdivision into smaller regions. For each of these regions, "pixel data was filtered with Gaussian derivatives on multiple scales, extracting texture features to classify each region" (130). In 388 chest X-rays collected from a TB screening program, where 37.9% of chest X-rays where abnormal, use of CAD had a sensitivity of 86%, a specificity of 50% and an area under the receiver operator characteristic (ROC) curve of 0.820. In a second data base of 200 chest X-rays where 50% were normal and 50% had interstitial disease, CAD demonstrated a sensitivity of 97%, a specificity of 90% with an area under the ROC curve of 0.986 (130).

Arzhaeva *et al* investigated the application of CAD in an adult TB screening program, in a cohort with normal chest X-rays, suspected cases and proven TB cases, using multi-valued dissimilarity measures (131). Compared to single-valued dissimilarities measures this approach retains more

information about local image features. The authors applied this approach locally and globally for each chest X-ray, and by merging local and global classification results into an overall opinion for the chest X-ray to be classified. Using a global and local multi-valued dissimilarity-based classification they found that the global dissimilarity approach achieved an area under the ROC curve of 0.810, while the fusion of local and global classifications increased the ROC curve to 0.830 (131).

2.7.4 Critical Literature Review of Computer Aided Diagnosis of Chest X-rays in Children

There are a limited number of paediatric trained radiologists in low income countries, including those with experience and certification in WHO standardized chest X-ray interpretation in children. The application of CAD in chest X-rays of children may be an interesting alternative and supplement to human reading (14, 127, 129). There is very limited literature on the application CAD for the detection and diagnosis of pulmonary pathology on chest X-rays in children (127).

Texture analysis is considered the most important radiographic feature of pneumonia on CAD. Oliveira *et al* used wavelet transforms for texture analysis to develop a prototype of CAD for chest X-rays in children, Pneumo-CAD, using a database evaluating *Haemophilus influenzae* type-b (HiB) vaccine in Brazil (132). The authors used WHO standardized chest X-ray interpretation methodology (15), and used 40 chest X-rays to train and 20 chest X-rays to test their software Pneumo-CAD, using the Haar wavelet. This generated the best results with a sensitivity of 100%, specificity of 80% and area under the ROC curve of 0.97 (132). However significant limitations of this study was the small sample size and the chest X-rays were photographed from a light box using a digital camera with low resolution and bit depth which limited the chest X-ray quality (132, 133). Photographing chest X-rays with a digital camera is

not consistent with the recommendations of the WHO on standardized chest X-ray interpretation in children, due to the significant loss in chest X-ray quality (15).

In a subsequent study the same group used Pneumo-CAD using the Haar wavelet and compared the findings in 5 contemporary machine learning classifiers. Again chest X-rays were photographed using a digital camera producing 8-bit gray scale images (134). Of the 156 chest X-rays used in this study, 78 had CXR-PEP using the WHO standardized chest X-ray interpretation criteria (15, 134). A 10-fold cross validation test was performed with each of the 5 classifiers. The Naïve Bayes classifier performed the best with a sensitivity of 96% and an area under the ROC curve of 0.95. Again the limitation of this study was the photographing of chest X-rays using a digital camera and the small sample size (15, 134).

Mouton *et al* assessed the application of CAD using a semi-automatic ASM, for the detection of pulmonary TB (clinical or laboratory confirmed) in 119 digital chest X-rays in children 0 to 5 years of which 113 had abnormalities (127). To allow for the training of classifiers in distinguishing between normal and abnormal regions, a radiologist manually outlined the ROI. The CAD chest X-ray output was a probability map for each image, indicating the degree of abnormality of every region in bilateral lung fields. The CAD classification produced an area under the ROC curve of 0.782 (95% CI 0.655 -0.937), averaged over all regions (127). Like Van Ginneken *et al* (130) only textural characteristics were used to classify images (127).

2.7.5 Limitations of Computer Aided Diagnosis of Chest X-rays

A limitation of many of the studies on CAD in chest X-rays is that the number of features used for classification or feature selection exceeds the number of positive cases with chest X-ray abnormalities. It is important for studies investigating the application of CAD in chest X-rays to

have larger sample sizes to validate the usage of CAD and for the development of better CAD schemes that use data for training (129).

There is limited literature on the application of CAD in chest X-rays in children (127). The studies by Oliveira *et al* are limited by the small sample size and the use of a digital camera to photograph chest X-rays which is against the recommendations of the WHO standardized chest X-ray interpretation, due to the significant loss of image quality (15, 132). Mouton *et al* investigating CAD for TB on chest X-ray in children, produced an area under the ROC curve of 0.782, and found that common errors with application of CAD on chest X-ray involved the peri-hilar areas of the lungs, especially the left lung (127).

The authors attributed this to the prominence of pulmonary vasculature in the peri-hilar areas, which could have been misclassified as pathology by CAD and to the limited number of abnormalities in the peri-hilar areas. Conversely when the radiologist defined increased broncho-vascular markings in the peri-hilar areas, the resulting CAD probability maps displayed limited abnormality. Compared to CAD, a trained radiologist takes into account a number of factors when making a diagnosis on chest X-ray, which is not always "quantifiable" by CAD (127).

3 Rationale for this Study

Pneumonia is among the leading infectious causes of morbidity and mortality in children less than 5 years of age globally (1-3). The chest X-ray remains the most readily available and the most common imaging modality for the assessment and diagnosis of CAP (14).

There is limited literature on paediatric chest X-ray quality and the impact of quality assurance interventions on chest X-ray quality, especially in non-industrialized countries with limited resources, including no paediatric trained radiographers or paediatric radiologists, and where chest X-rays are not routinely reported by radiologists. Certain paediatric chest diseases may "mirror radiographic noise", which highlights the need for optimal and consistent image acquisition protocols and practices to enable radiologists and clinicians to differentiate between actual disease like pneumonia from poor quality chest X-rays (25, 26). Findings and recommendations for paediatric chest X-ray optimization from this study outcome will be made to the WHO CRES committee.

Chest X-ray abnormalities are common in hospitalized children with CAP (59-62), with air space/alveolar consolidation the most common finding 40-75%, followed by interstitial infiltrates 9-54% (59-62). There have been significant advances in South African child health in recent years including incorporation of the Integrated Management of Childhood Illness Guidelines in Primary Care, adoption of coverage for Hib and pneumococcus in the EPI (31, 135) and updated South African National ART guidelines for the prevention and treatment of HIV infection in infants and children (106). The last pneumonia etiology studies were conducted in Soweto more than a decade ago, prior to the introduction of bacterial conjugate vaccines and

ART (62). The impact of ART and bacterial conjugate vaccines on chest X-ray findings in a high HIV prevalence setting in children hospitalized with WHO-defined severe or very severe pneumonia has not been described to date.

There is conflicting literature on the association between clinical parameters and chest X-ray patterns in children. Clinical parameters like fever, tachynea and hypoxia have been shown to be associated with air space disease (70-75, 77, 78). This contradicts other studies that found no association between any of the clinical parameters like tachypnea, hypoxia, fever and chest X-ray patterns (61, 75, 79-81). Lack of standardized chest X-ray reporting methodology and variability in terminology is a significant limitation of these studies. Furthermore most of these studies were not performed in a South African setting, with a high HIV burden. The association between chest X-ray patterns and CRP, fever, tachypnea, hypoxia has not been described in HIV-infected and HEU children hospitalized with WHO-defined severe or very severe pneumonia in the era of access to bacterial conjugate vaccines.

There is conflicting literature on the utility of chest X-rays in determining microbiological etiology in children with pneumonia. Most studies investigating the association between chest X-ray patterns and microbiological etiology were performed in industrialized countries (63-65, 68, 69, 94) , where the spectrum of pathology may differ significantly from developing countries, especially sub-Saharan Africa. Furthermore these previous studies are limited by small cohort size (63, 68, 69, 94), limited number of microbes investigated (63, 64, 68, 69), the inclusion of both ambulatory and hospitalized children (63, 64), reporting of chest X-rays by a single radiologist (62, 68, 94), lack of standardized chest X-ray reporting of air space consolidation and interstitial infiltrate and the heterogeneity of microbiological methods used without a gold standard. It remains important to investigate the diagnostic utility of chest X-rays, using a panel

of readers, in determining microbiological etiology in the era of routine immunization with PCV, using advanced novel molecular diagnostics which to date has not been investigated on children in this setting.

There are limited radiologists worldwide, especially in low income countries, hence clinicians often have to interpret chest X-rays. WHO developed a standardized chest X-ray interpretation for bacterial VE trials and pneumonia epidemiological studies in children, but there are a number of current limitations including "significant drift" in the application and maintenance of WHO standards, despite the WHO training module. Hence there is an international need for the development of a novel software on CAD for WHO standardized chest X-rays interpretation, especially in settings where there is limited clinical expertise in the interpretation of paediatric chest X-rays. This may prove pivotal in research in improving the quality of health care in children in developing countries.

To address the limitations to our current understanding of paediatric pneumonia etiology and how this may impact on chest X-ray findings in children the series of studies described in this thesis were undertaken within the context of the Pneumonia Etiology Research for Child Health (PERCH) project. Also included was the development of a digital framework of paediatric chest X-ray interpretation which is reproducible and not dependent on varying opinions of clinicians and radiologists. The PERCH project is a prospective multi-centre international case-control study designed to establish which pathogens are causative of WHO-defined severe and very severe pneumonia in hospitalized children (cases) between 28 days to 59 months of age in the developing world (136). The 9 sites, 7 countries included in the PERCH study are Bangladesh,

The Gambia, Kenya, Mali, South Africa, Thailand and Zambia .The PERCH study used rigorous standardized definitions and clinical and laboratory protocols (137).

To address the current limited literature on paediatric chest X-ray quality and the impact of quality assurance interventions on chest X-ray quality, we prospectively evaluated chest X-ray quality from the PERCH study in the 7 developing countries (136) and we determined the impact of quality assurance activities on chest X-ray quality over the 14 month study period.

As the introduction of the HibCV and PCV vaccine have reduced the main etiological causes of childhood community acquired pneumonia, the burden of unknown causes of pneumonia may have a significant contributory role (138). A significant limitation of studies on microbiological etiology is the poor sensitivity of diagnostic methods used (137, 139). Comprehensive microbiological testing within the context of a case-control study design is the core principle of the PERCH study. Molecular diagnostics like multiplex polymerase chain reaction (PCR) on nasopharyngeal-oropharyngeal (NPOP) swabs, induced sputa (IS), endotracheal aspirates (ETT) and lung aspirate (LA) were used in PERCH due to increased sensitivity achieved by combining amplification and detection in one reaction tube and allowing for several target assays simultaneously (137, 139).

4 Aim and Objectives of this PhD thesis

4.1 Aim of this PhD research

The aim of this PhD research was to determine chest X-ray quality and diagnostic utility in children under 5 years hospitalized with community acquired pneumonia in the era of bacterial conjugate vaccines, antiretroviral therapy, molecular diagnostics and computer aided diagnosis

4.2 The objectives of this PhD research were:

Within the context of the PERCH 7 country study:

1. To assess quality of chest X-rays in each of the 9 PERCH sites (in 7 countries) over a 14 month period by quantifying radiographic errors through use of a customized quality assessment form and to determine the impact of quality assurance activities on chest X-ray quality during the course of the chest X-ray quality assurance period in each of the 9 sites

Within the context of the PERCH South African site:

2. To describe and compare chest X-ray patterns in HIV-unexposed, HIV- exposed-uninfected (HEU) and HIV-infected children 28 days to 59 months of age hospitalized with WHO-defined severe or very severe community acquired pneumonia, and to determine the association between HIV-exposure status and chest X-ray patterns

3. To determine the association of chest X-ray patterns with clinical symptoms and signs, HIV exposure status, acute phase reactants and clinical outcomes in children hospitalized with WHO-defined severe or very severe community acquired pneumonia

4. To determine the association of specific chest X-ray patterns with the PERCH Quantitative Analysis (PQA) model predicted high probability of bacterial, respiratory virus and *Pneumocystis jiroveci* associated pneumonia, microbiologically confirmed pneumococcal pneumonia (MCPP), culture confirmed pulmonary TB and culture or clinically confirmed pulmonary TB in HIV-unexposed, HEU and HIV-infected children hospitalized with WHO-defined severe or very severe community acquired pneumonia.

5. To determine the sensitivity and specificity of computer aided diagnosis (CAD4WHOKids) for chest X-ray primary end-point pneumonia (CXR-PEP) versus non CXR-PEP compared to a consensus human interpretation used a reference standard.

Dr Mahomed's proposal for objective 1, which involves all 9 PERCH study sites, was approved by the PERCH executive committee. The PERCH executive committee granted Dr Mahomed permission to use this data for her PhD thesis and publications.

Objectives 2 to 5 are nested within the South African PERCH site, which study Professor Madhi is the principal investigator. He has full publishing rights to the data outlined in these objectives and has granted Dr Mahomed permission to use these data for her PhD thesis and publications.

Professor Madhi is in agreement that the data outlined in the objectives above may be used by Dr Mahomed to contribute towards the requirements for a Doctor of Philosophy (PhD) in the School of Clinical Medicine (Diagnostic Radiology) through the University of the Witwatersrand. This PhD is supervised by Prof Madhi and co-supervised by Dr Moore (clinical lead on the South African PERCH site).

5 Methods and Materials

5.1 Study setting: The PERCH Study

The PERCH study is a prospective multi-centre, international case -control study designed to establish which pathogens are causative of WHO defined severe and very severe pneumonia in hospitalized children (cases) between 28 days and 59 months of age in middle and low income countries (136). The PERCH study was conducted in 9 sites (10 hospitals) in 7 countries, namely Bamako (Mali), Basse (The Gambia), Dhaka (Bangladesh), Johannesburg (South Africa), Kilifi (Kenya), Lusaka (Zambia), Matlab (Bangladesh), Nakhon Phanom (Thailand) and Sa Kaeo (Thailand). Objective 1 is nested within the 7 country PERCH study. The PERCH study used rigorous standardized definitions and clinical and laboratory protocols in all 7 countries (137).

5.1.1 Study Setting: The PERCH Study South African Site

The PERCH South African site in which objectives 2 to 5 are nested is based at Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg. CHBAH is the largest hospital in the Southern Hemisphere with 450 paediatric beds, and at the time of the study was the sole public referral hospital for 23 primary health care clinics in Soweto. All the primary health care clinics do routine immunizations according to the South African EPI, and none of the clinics admits children with WHO-defined severe or very severe pneumonia.

5.2 Inclusion and Exclusion Criteria of the PERCH study

5.2.1 Inclusion criteria:

Cases met the following inclusion criteria:

- Admitted to hospital
- Had clinical features of WHO severe or very severe pneumonia
- Had a chest X-ray taken within 72 hours of hospitalization
- Resident in defined study catchment area
- Aged 28 days-59 months (the day of birth was considered to be "day 1"; thus a child born on September 1st was considered to be 28 days old on September 28th)
- Written informed parental/guardian consent obtained

WHO clinical criteria for severe and very severe pneumonia are defined as the presence of cough and/or difficulty breathing with the current illness and lower chest wall in-drawing (LCWI) and/or danger signs (140) reference inserted (refer Table 5.1).

Table 5.1 WHO-Defined Clinical Criteria for Severe and Very Severe Pneumonia (140) (Ref)

Classification	Cough or difficulty breathing plus at least one of the following signs or symptoms
Severe Pneumonia	Lower chest wall in drawing (LCWI)
Very Severe Pneumonia*	Central cyanosis, unable to feed , vomiting everything convulsions, lethargy, unconsciousness or head nodding

* Definitions for certain signs for the age group 28-59 days were modified as follows:

1. Lethargy was defined as "an infant who does not wake up on stimulation or, on waking, subsequently moves only on stimulation or does not move at all";

2. Unable to drink/breastfeed was modified to “difficulty feeding or not feeding well (in an infant who was previously feeding well)”

5.2.2 Exclusion criteria:

Cases that meet any of the following exclusion criteria were considered to be ineligible for enrolment in PERCH:

- Hospitalized for any cause within the last 14 days
- Enrolled as a PERCH case within the past 30 days
- Resolution of lower chest wall in-drawing following bronchodilator therapy in children hospitalized with severe pneumonia and wheeze ie: after one dose in children < 2 years or three doses in children 2-5 years
- Children enrolled into PERCH that had no results for any study specimen were excluded from the primary etiology analysis

5.3 Community Controls

During the two year study period, cases with WHO-defined severe or very severe pneumonia were enrolled with healthy community controls that were age frequency and HIV-status matched to cases. Chest X-rays were not performed in controls in this study due to increased burden of radiation being an ethical concern. Therefore, the analyses described in this thesis do not include information from any of the PERCH controls.

5.4 Data Centralization

The PERCH project database is centralized at EMMES Corporation (Rockville, Maryland, USA). The clinical, immunological and inflammatory marker parameters and pathogen specific data for this study were accessed through the EMMES Corporation for this study with

permissions from the PERCH Analysis Team, based at the International Vaccine Access Centre (IVAC), Johns Hopkins School of Public Health, Baltimore, Maryland, USA.

5.5 Enrolment of cases in each of the 7 country PERCH study

Participant enrolment in the PERCH study was staggered by site. Johannesburg (South Africa) and Kilifi (Kenya) commenced in August 2011, Lusaka (Zambia) in October 2011, Basse (The Gambia) in November 2011, Bamako (Mali), Nakhon Phanom and Sa Kaeo (Thailand), and Dhaka and Matlab (Bangladesh) in January 2012. Each site enrolled cases prospectively for 24 months. Over the 24 month period the number of cases enrolled in the PERCH study with WHO-defined severe or very severe pneumonia in each of the 7 countries was as follows: South Africa 920 cases, Mali 674 cases, The Gambia 638 cases, Kenya 634 cases, Zambia 617 cases, Bangladesh 525 cases and Thailand 224 cases.

5.6 Methods: To assess the quality of chest X-rays in each of the 7 countries in PERCH study and determine the impact of quality assurance activities

5.6.1 Detailed Description of the Radiology Departments in each of the 7 country, 9 site PERCH Study

Each site used one hospital except the Dhaka (Bangladesh) site, which used 2 hospitals ICDDR-B and Monowara, with 83% of total PERCH chest X-rays performed in the ICDDR B hospital. The results of the 2 hospitals used in Dhaka (Bangladesh) site are combined for this study. Table 9.1 summarizes the radiology departments in each of the study sites. Only one site Bamako (Mali) is a dedicated pediatric hospital, and only 3 out of the 9 sites including Bamako (Mali), Johannesburg (South Africa) and Lusaka (Zambia) have dedicated paediatric radiology departments where children are X-rayed separately from adult patients. Johannesburg (South Africa) has 12 radiologists servicing the 3200 bed hospital, and only 1 radiologist is allocated to the paediatric radiology department per day on a rotational basis.

Two sites Lusaka (Zambia) and Matlab (Bangladesh) used analogue X-ray units for the full duration of the study, while Nakhon Phanom (Thailand) transitioned from an analogue to digital X-ray unit, 6 months into the study period. Johannesburg (South Africa) had 2 digital X-ray units during this study; but chest X-rays were printed and scanned for 11 out of the 14 month study period as the software to store digital chest X-rays were not yet operational.

None of the 10 hospitals had paediatric trained radiographers and the number of onsite radiologists in the various departments varied between 0-3. The average number of pediatric X-rays performed per day ranged from 5 to 58 in each of the 10 hospitals. X-rays were routinely reported by an onsite radiologist in only 2 hospitals; ie: Bamako (Mali) Hospital Gabriel Toure and Dhaka (Bangladesh) Monowara Hospital; refer Table 5.2

Table 5.2: Detailed Description of the Radiology Departments in each of the 7 country, 9 site PERCH Study

Site (Country)	Hospital Type	Paed Beds	X-ray Unit	Paediatric Trained Radiographers	Children X-rayed with adults	Average no of Pediatric X-rays done per day	X-Rays Reported by radiologist	No of Radiologists On Site
Bamako (Mali) Hospital Gabriel Toure	Pediatric	143	Digital	no	no	15	yes	3
Basse (The Gambia) Basse Health Centre	Adult and Pediatric	25	Digital	no	yes	12	no	0
Dhaka (Bangladesh) Hospital ICDDR-B	Adult and Pediatric	350	Digital	no	yes	30	no	1
Dhaka (Bangladesh) Monowara Hospital	Adult and Pediatric	32	Digital	no	yes	15	yes	1
Johannesburg (South Africa) Chris Hani Baragwanath Academic Hospital	Adult and Pediatric	450	Digital	no	no	58	no	1 (12 in total)
Kilifi (Kenya) KEMRI-Welcome Trust Research Centre	Adult and Pediatric	54	Digital	no	yes	10	no	0
Lusaka (Zambia) University Teaching Hospital	Adult and Pediatric	346	Analogue	no	no	40	no	3
Matlab (Bangladesh) Hospital ICDDR, B	Adult and Pediatric	85	Analogue	no	yes	5	no	0
Nakhon Phanom (Thailand) Nakhonphanom hospital	Adult and Pediatric	74	6 months Analogue, 8 months Digital	no	yes	15	no	2
Sa Kaeo (Thailand) Crown Prince General Hospital	Adult and Pediatric	69	Digital	no	yes	20	no	1

5.6.2 Study Period for Chest X-Ray Quality Assessment in Nine Site PERCH Study

Chest X-ray quality assessment for this study was performed prospectively for all sites over a 14 month period from October 2012 to November 2013. For the purposes of this study chest X-ray quality was assessed for individual site by the city, example Johannesburg in South Africa. Therefore the city will be referred to henceforth in this PhD thesis.

5.6.3 Rationale for Frontal and Lateral Chest X-Rays performed in Johannesburg

In 8 out of the 9 PERCH sites only frontal chest X-rays were routinely performed in children investigated for pneumonia; hence quality assessment was performed on frontal chest X-rays only. In Johannesburg both frontal and lateral chest X-rays are performed in children because of a high burden of childhood pulmonary TB (36, 102); hence quality assessment was done on both frontal and lateral chest X-rays. Superimposed bacterial pneumonia is thought to be common in children with underlying PTB in this setting (39, 141). Routine lateral chest X-rays are performed in children in South Africa as they may improve the detection of lymphadenopathy in children investigated for PTB (142).

5.6.4 Monthly Uploading Procedures of Chest X-Rays, and Selection of Chest X-Rays for Quality Assessment

Depending on the study site either digital chest X-rays or analogue chest X-rays that were scanned to a digital format (refer Table 5.2) were uploaded from each of the 9 sites into an online database (EMMES Corporation, Rockville, Maryland, USA) on a monthly basis during the full course of the study. Only the chest X-rays uploaded during the 14 month chest X-Ray quality assurance period will be described in this study objective. From the monthly uploads to the EMMES Corporation STATA software (StataCorp, College Station, Texas, USA), 10 chest X-rays were randomly selected from each of the 9 study sites every month during the study period, for quality evaluation in this study. If less than 10 chest X-rays were uploaded for the month by a

particular site, then all chest X-rays uploaded for that month were selected for quality assessment. This process was facilitated by Mr Gong.

5.6.5 Customized Chest X-ray Quality Assessment

Over the 14 month study period an external paediatric radiologist Dr Manduka, assessed chest X-ray quality with a customized forced choice tick sheet using 6 parameters developed from the European guidelines on quality criteria for diagnostic radiographic images (143) and the modified parameters developed by Cook *et al* (22). The 5 parameters assessed included positioning, collimation, exposure, inspiration and processing and are described in detail in Table 5.3. For processing we included problems with scanning analogue chest X-rays to a digital format. For the 6th parameter motion yes or no was assigned. The external reviewer was blinded to all the clinical information, except the month of chest X-ray examination and the study site. Refer to appendix 3 for the template used for the customized chest X-Ray quality assessment.

Table 5.3: Customized Chest X-ray Quality Assessment

Parameter	**Good**	**Fair**	**Bad**
Positioning	Perfectly straight	Mild rotation but diagnostic	Marked rotation and non-diagnostic
Collimation	Optimum Collimation	Wide collimation but not including other body parts	Wide collimation including other body parts/organs or over collimation with normal chest anatomy cropped
Exposure	Optimum with visualization of trachea, main bronchi and vascular pattern in	Suboptimal only major anatomy visible but diagnostic	Either overexposed or underexposed and non-diagnostic

	two-thirds of lungs		
Inspiration	Well inspired > 6 anterior ribs	Under inspired < 6 anterior ribs but diagnostic	Under inspired < 6 anterior ribs and non-diagnostic
Processing	Optimum	Suboptimal (eg: roller marks from processor) but diagnostic	Non diagnostic

5.6.6 Chest X-ray Quality Assurance Activities at Each of the 9 Sites in Response to the Feedback

The external radiologist chest X-ray quality assessment reports were sent back to each site on a monthly basis. This individual site feedback was designed so that each site/radiology department could identify problematic parameters in maintaining chest X-ray quality and identify areas for improvement, by providing feedback to radiographers and radiologists in their respective departments. The individual sites were also asked to provide feedback on the monthly chest X-ray quality assessment reports. Refer Appendix 3. Challenges and limitations in obtaining good chest X-ray quality were thus identified in each site.

For the purposes of the current report, specific quality assurance interventions and responses for each PERCH study site were evaluated through communication with the radiologist/clinician responsible for chest X-ray data collection and quality control at each PERCH site by the principle investigator of this study Dr Mahomed. The site specific interventions were verified by the external radiologist Dr Manduka, and are summarized in Table 5.4.

Table 5.4 Chest X-ray Quality Assurance Activities at Each of the 9 Sites PERCH study in Response to the Quality Assessment Feedback

Site (Country)	Chest X-ray Quality Assurance Activities
Bamako (Mali)	Training of radiographers on chest X-ray quality assurance at start of study and at 6 monthly intervals. Chest X-ray quality checks performed weekly by radiologist. PERCH chest X-ray quality assurance report feedback given to radiographers as a group on a monthly basis. Six months into the study all chest X-rays were assessed for diagnostic and quality assessment by internal radiologist.
Basse (The Gambia)	Existing quality assurance program for all radiographs performed in department. Training and supervision of radiographers performed by senior radiographer from the Medical Research Council, including quality control of a random selection of radiographs every 3 months. Reading of all chest X-rays for diagnostic and quality assessment done by study clinicians, feedback in real time to radiographers on quality. Feedback to radiographers on PERCH quality assessment reports monthly.
Dhaka ICDDR, B (Bangladesh)	Monthly discussions of the PERCH chest X-ray quality assessment reports with the radiographers and radiologist in the radiology department, with group and individual feedback. PERCH chest X-rays read by PERCH study clinicians using a customized report, with feedback to radiographers.
Dhaka Monowara (Bangladesh)	Routine reporting of all plain radiographs by radiologist. PERCH chest X-ray quality assessment monthly feedback given to radiologists and radiographers at this site
Johannesburg (South Africa)	Dedicated radiographers allocated to paediatric radiology department during office hours. Discussion of the monthly PERCH quality assessment reports with the radiographers in the paediatrics radiology department. Approximately 10% of PERCH chest X-rays read by radiologist using a customized report and feedback on chest X-ray quality given to radiographers at informal meetings during study.
Kilifi (Kenya)	Monthly chest X-ray quality assurance meetings, regarding PERCH feedback. Individual feedback as radiographers had to sign against all plain radiographs they performed. PERCH quality feedback recommendations applied across the board, since they were generalizable to all radiographs.
Lusaka (Zambia)	Each month the PERCH quality assessment reports were discussed with the chief radiographer and radiographers in the department. Feedback on chest X-ray quality was both done individually and as a group and focussed on characteristics of 'good' quality images, and the mistakes that led to the 'poor' quality images. Radiographers with more experience in paediatric imaging trained junior radiographers in portable analogue X-ray unit usage in children. Damaged and dirty screens were cleaned or replaced during the course of the study.
Matlab (Bangladesh)	Discussion of the PERCH quality assessment reports with the one radiographer on site every month. PERCH CXRs read by PERCH study clinicians using a customized report and feedback on quality of CXRs given to radiographer.
Nakhon Phanom (Thailand)	Monthly feedback on PERCH quality assessment reports given to radiographers. Overexposure to abdomen and pelvis was one of the site's concerns: study procedures were communicated with paediatricians, radiologist and radiographers. PERCH study clinician assessed PERCH CXR quality and provided routine feedback to radiology department.
Sa Kaeo (Thailand)	Plain radiographs not routinely read by radiologist. But all PERCH CXRs were routinely reported by on site radiologist and feedback was given in real time to radiographers on chest X-ray quality. Monthly feedback on PERCH quality assessment reports that where sub-optimal given to radiographers and these CXRS quality errors were discussed.

5.6.7 Chest X-Ray Quality Assessment Scoring System

For each of the 5 parameters of positioning, collimation, exposure, inspiration and processing, as described in Table 9.2, an arbitrary score of 2= good, 1=fair and 0=bad was assigned. For the 6th parameter motion an arbitrary score of 1= no motion and 0=motion was assigned. The maximum score that chest X-rays were assessed was out of 11. To evaluate the effect of quality assurance activities in each of the 9 sites over the 14 month period, a test for trend analysis was performed using the combined arbitrary scoring system on a month to month basis.

5.6.8 Statistics for Chest X-Ray Quality Assessment

Data were analysed using STATA software, version 13.0 (StataCorp, College Station, Texas). The number and percentage of good, fair and poor chest X-rays for each of the 6 parameters as delineated by Table 9.2 was determined for each site. The impact of the PERCH chest X-ray quality assurance activities was inferred by conducting a test-for-trend analysis for the combination of all 6 parameters during each month of the study. This was done on a site-by-site basis, and for all sites combined. Statistical significance was set as a two-tailed *p*-value of <0.05 as per standard practice.

5.6.9 Ethics for Chest X-Ray Quality Assessment in the PERCH study

Ethics approval for use of the chest X-ray quality assurance data from all 9 PERCH sites, 7 countries' was obtained from the Johns Hopkins School of Public Health IRB approval No: 0000307 and the PERCH Executive Committee who approved this study.

5.7 Detailed Description of the X-Ray Units in Paediatric Radiology at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg

The radiology department at Chris Hani Baragwanath Academic hospital has a dedicated paediatric radiology unit, where X-rays, ultrasonography and fluoroscopy in children are performed. The paediatric radiology department is equipped with 2 digital X-ray units, Philips and Second Opinion. The paediatric admissions ward has a portable analogue X-ray unit, Shimadzu, while the paediatric X-ray room in the maternity unit has an analogue X-ray unit, Shimadzu. Refer Table 5.5 below for the full details of the X-ray units.

Table 5.5 Description of Radiography Units used for Children at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg

Location	**Analogue or Digital**	**Make**	**Type Model**	**Capacity**	**Year of Installation**
Paediatric Radiology Department	Digital	Philips	MD Eleva	kVp* 140 MAS# 300	2010
Paediatric Radiology Department	Digital	Second Opinion	N64 HF	kVp* 125 MAS# 320	2011
Paediatric Admissions Ward	Portable Analogue	Shimadzu	Carltex U MU 125 P	KVp*125 MAS# 200	1999
Maternity Unit Paediatric X-ray room	Analogue	Shimadzu	R-20	KVp* 150 MAS# 200	1998

*kVp- kilo volt peak

#MAS-milliampere-seconds

5.8 Staffing in Paediatric Radiology at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg

Two dedicated radiographers with approximately 3 student radiographers are allocated to the paediatric radiology unit routinely during office hours Monday to Friday 8 am to 4 pm. After hours radiographers are allocated to the paediatric radiology unit on a rotational basis, so expertise in obtaining images from pediatric patients is not consistent over after-hours shifts. One radiologist and radiology registrar-in-training are allocated to the paediatric radiology unit on a rotational basis during office hours. Plain radiographs are not routinely reported by the radiologist due to staff shortages, high patient load and the need for reporting of other imaging modalities like sonar, fluoroscopy, CT and magnetic resonance imaging (MRI) studies. Clinicians interpret all plain radiographs and only discuss certain cases with radiologists during formal and informal consultations with the paediatric radiology unit.

5.9 Chest X-ray Imaging Procedures of Children at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg

As per standard of care at CHBAH all routine X-rays in children are performed in the paediatric radiology unit. If children are clinically unstable to be taken to the radiology unit, the clinician will order a portable chest X-ray to be performed in the paediatric admissions ward. In this study we did not differentiate between digital chest X-rays taken in the paediatric radiology unit and analogue portable chest X-rays taken in the wards.

Chest X-rays were performed as per routine standard of practice in the paediatric radiology unit at CHBAH. In children < 9 months supine frontal chest X-rays were performed, while in children $\geq$ 9 months erect chest frontal chest X-rays were performed. However this guideline was dependent on the clinical status of the child. South Africa has a high burden of childhood PTB (36, 102). Superimposed PTB is common in children hospitalized with bacterial or respiratory

viral pneumonia (39, 141). Routine lateral chest X-rays in addition to frontal chest X-rays were performed in children investigated for associated PTB, as they may improve the detection of lymphadenopathy (142). Only frontal and lateral chest X-rays (were available), taken within 72 hours of admission were included in this study to avoid reporting on possible nosocomial infections. When multiple chest X-rays were taken for the same patient the first interpretable chest X-ray was used in this study as determined by the principle investigator.

5.10 Chest X-Ray Storage and Archiving at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg

Although the paediatric radiology unit has 2 digital X-ray units, chest X-rays were routinely printed and manually scanned (using an Epson Expression 10000 XL flatbed scanner) from 17 August 2011 to 30 June 2013 due to the absence of software to upload and store the digital chest X-rays directly. During the period from July 2013 to August 2013 some of the chest X-rays were stored directly from the newly installed picture archiving computerized system (PACS) system. Chest X-rays were stored digitally as Joint Photographic Experts Group (JPEG) images, with 256 grey levels (8 bit), and uploaded onto the EMMES database via Dropbox on a monthly basis during the course of the study.

5.11 Detailed Chest X-Ray Interpretation using the Fleishner chest X-ray glossary of terms and WHO standardized chest X-Ray definitions

Recognizing that the WHO standardized chest X-ray interpretation was designed for the main purpose of standardizing chest X-ray interpretation for bacterial vaccine efficacy trials and epidemiology studies in children, we undertook detailed interpretation of chest X-rays using the Fleishner chest X-ray glossary of terms and WHO standardized chest X-Ray definitions (15, 144) to develop the customized chest X-ray reporting form; refer Table 5.6 and Appendix 4. We used the WHO standardized chest X-ray conclusions of CXR-PEP and other infiltrate as main

chest X-ray outcome measures as described in Table 1.1, in order to compare our results to the literature findings on pneumonia epidemiological studies and to accurately follow chest X-ray pneumonia epidemiological trends over time (15). The limitation of the Fleishner chest X-ray glossary of terms is that these were developed for both adult and children (144) and beside the WHO standardized chest X-ray interpretation criteria (15), there is no other current internationally accepted standardized chest X-ray interpretation criteria for children under 5 years.

Air space consolidation was defined as "homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls", which may be associated with air bronchograms (144). Pleural effusion was defined using WHO standardized chest X-ray interpretation criteria, defined as "fluid in the pleural space in the lateral pleural space, between the lung and chest wall, may be at the costophrenic angle or as a layer adjacent to the lateral chest wall, but not in the horizontal or oblique fissures" (15). CXR-PEP was defined as air space disease and/or pleural effusion (15). Importantly, plate atelectasis was not considered as air space consolidation. Collapse/atelectasis was defined as decreased volume associated with increased opacity, displacement of fissures, bronchi, vessels or mediastinum on chest X-ray. The distribution of collapse can be lobar, segmental or sub-segmental (144).

The WHO standardized definition of other infiltrate was used as the main category (15), and Fleishner chest X-ray glossary of terms for the descriptors of this chest X-ray pattern, refer Table 3.8 and Appendix 4. Ground glass infiltrate was described as an area of "hazy increased lung opacity within which margins of pulmonary vessels may be indistinct". In comparison to consolidation ground glass opacification is less opaque than consolidation and broncho-vascular margins are not obscured (144). Reticular infiltrate on chest X-ray represents interstitial lung

disease and was defined as “a collection of innumerable small linear opacities that result in an appearance resembling a net”. Nodular pattern was characterized on chest X-ray is defined “by the presence of innumerable small rounded opacities that are discrete and range in diameter from 2 to 10 mm”. Miliary infiltrate was defined as “profuse, tiny, discrete, rounded pulmonary opacities less than 3 mm in diameter; that are uniform in size and diffusely distributed on chest X-ray”. Reticulo-nodular infiltrate was defined as a combination of reticular and nodular pattern, “with the summation of points of intersection of innumerable lines, creating superimposed micro nodules on chest X-ray” (144).

Pleural plaque was defined as a “well-demarcated area of pleural thickening either flat or nodular lesions which may have calcification”. Pneumothorax is due to air in the pleural space, resulting in a visceral pleural edge (144).

Bronchiectasis was defined as “bronchial dilatation with respect to the accompanying pulmonary artery and lack of tapering of bronchi”. Cavity was defined as a “gas-filled space, seen as a lucency or low-attenuation area, within pulmonary consolidation, a mass or a nodule” (144).

Lymphadenopathy definitions: the doughnut sign was defined as lobulated, oval, dense masses filling the hilar points on the frontal chest X-ray and forming a characteristic ring, the doughnut sign, on the lateral chest X-ray. The doughnut sign on lateral chest X-ray represents superimposed hilar and subcarinal lymphadenopathy, and is formed anteriorly and superiorly by the normal right and left main pulmonary arteries and the posterior aspect of the aortic arch and inferiorly by the hilar and subcarinal lymphadenopathy. The radiolucent centre of the doughnut is formed by the trachea and upper lobe bronchi (145, 146).

As the 3 readers were blinded to all clinical information including the age of the child, cardiomegaly was defined as a cardio-thoracic ratio ≥50%. The chest X-rays were reported using the customized report form, described in Table 5.6 and Appendix 4.

Table 5.6 Chest X-Ray Pattern and descriptors used in this study

Chest X-ray Pattern	**Descriptors of Chest X-ray Patterns**
Airspace disease	Segmental/sub segmental consolidation Lobar consolidation Multi-lobar consolidation Volume loss/lung collapse Expansion/bulging fissure Lung abscess
Pleural disease	Pleural effusion Pneumothorax Pleural plaques/calcification
Chest X-ray primary end-point pneumonia (CXR-PEP)	Air space disease and/or pleural effusion May include cases in which airspace disease coexisted with other infiltrate
Other infiltrate	Peribronchial thickening Reticulo-nodular infiltrate Reticular infiltrate Miliary infiltrate (nodules < 3mm) Large nodular infiltrate (nodules > 3mm) Perihilar streakiness Ground glass infiltrate
Other infiltrate only	Other infiltrate without CXR-PEP

Chronic lung disease	Bronchiectasis Cavities Fibroses
Intrathoracic lymphadenopathy	Hilar or mediastinal masses Hilar elevation Mediastinal shift Tracheal or bronchial compression Unilateral air-trapping Lobar collapses Doughnut sign
Bilateral air trapping	Greater than 6 anterior ribs visible at mid-diaphragm level and flattening of the diaphragm and increased retrosternal air on lateral chest X-ray
Cardiomegaly	Cardio-thoracic ratio ≥50%
Normal chest X-ray	Absence of airspace disease, pleural disease, other infiltrate, chronic lung disease, lymphadenopathy and bilateral air trapping
Uninterpretable chest X-ray	Chest X-ray not interpretable with regards to the presence or absence of CXR-PEP or other infiltrate

5.12 Distribution of air space disease and other infiltrate

The distribution of the radiographic patterns of air space disease and other infiltrate was evaluated on chest X-ray as described by Pitcher *et al* ie: by dividing each lung into 3 zones: upper, middle, lower zone. Disease was considered focal if confined to 1 zone, multi-focal if involving 2-4 zones and diffuse if >4 zones were involved (14). This categorization of focal, multi-focal and diffuse pattern was performed during the data analysis phase from the zone descriptors on the customized report form, refer Appendix 4.

5.13 Chest X-Ray Independent Reading Procedures

Chest X-rays were read independently by 3 radiologists (Drs N. Mahomed, T Sewchuran and H Moodley), with Dr Mahomed having more clinical experience in paediatric radiology and WHO standardized chest X-ray interpretation, compared to the other 2 readers who had similar level of experience. All 3 readers have experience in the interpretation of chest X-rays in a high HIV prevalence setting and similar scope of clinical practice. The 3 readers were blinded to the clinical, laboratory and immunological findings and interpreted the chest X-rays independently.

Prior to chest X-ray interpretation for this study all 3 readers undertook standardization training using the set of 220 chest X-rays from the WHO standardization training module (15). The relevant publications (15, 144-146) were provided to the readers and a separate chest X-ray training set was developed by Dr N. Mahomed from CHBAH paediatric radiology library to standardize chest X-ray pattern readings of lymphadenopathy, chronic lung disease and bilateral air trapping. The majority consensus reading (2 out of 3 or 3 out of 3 readers) for each chest X-ray pattern and each chest X-ray pattern descriptor was used. This was only performed at the end of the chest X-ray reading period, during the data analysis phase.

5.14 HIV Exposure Definitions

HIV exposure definitions were derived by evaluation of HIV serologic (enzyme-linked immunosorbent assay (ELISA) and/or HIV rapid tests) and molecular test results (i.e., HIV PCR and/or HIV viral load), maternal HIV serologic results (where available) and maternal HIV status in pregnancy. HIV status and exposure categories are tabulated in Table 5.7.

Table 5.7 HIV exposure and infection categorization

HIV Exposure Status	**Definitions**
HIV-infected	1. HIV PCR positive 2. ELISA test positive in any child ≥ 12 months of age
HIV Negative	1. HIV PCR negative in a child <18 months of age 2. HIV ELISA negative in a child, regardless of age group 3. If the child was untested for HIV, the maternal HIV ELISA test results at the time of PERCH enrolment are negative
HIV-Exposed	1. Child is HIV positive (as determined from the HIV derived variable, above) 2. ELISA result positive 3. Maternal HIV history during pregnancy documented to be positive regardless of the age of the child 4. Maternal history during pregnancy was reported (not documented) to be positive and the child was <7 months with a positive ELISA result 5. Maternal history during pregnancy is reported (not documented) to be positive and the child is ≥ 7 months, regardless of child's ELISA result 6. Maternal history after pregnancy (documented) is positive or she had a positive ELISA at the time of the child's PERCH enrolment (only applies to children ≤6 months)
HIV-Exposed, Uninfected (HEU)	1. Child fulfils criteria for inclusion in 'HIV Exposed' category (above), but is confirmed to be HIV Negative on confirmatory testing: a) Negative HIV PCR or HIV viral load in a child <18 months of age; b) Negative HIV ELISA in a child ≥18 months of age

HIV-unexposed	1. Documented negative status for mother during pregnancy, after pregnancy, or at PERCH enrolment 2. Negative ELISA among children <7 months 3. Negative ELISA among children ≥7 months whose mother is documented to be HIV negative
HIV Presumed Unexposed	1. If child is ≥7 months with negative ELISA test result (and not on antiretroviral treatment) and maternal history is reported (but not documented) to be negative
HIV Unknown Exposure, Uninfected	1. If maternal history is missing or unknown 2. HIV PCR negative in a child <18 months of age 3. HIV ELISA negative in a child, regardless of age group
HIV Exposure Unknown	4. If maternal history is missing or unknown 5. Childs HIV ELISA result missing or indeterminate 6. No documented HIV test result for children (unless he/she falls into one of the above categories)

5.14.1 HIV-infected Children Immune categorization

In HIV-infected children the revised 2006 WHO immunological classification in children based on CD4 percentage or absolute count was used (147). Based on this classification children are classified as having not significant, mild, advanced or severe immune suppression. The WHO classification in children is summarized in Table 5.8.

Table 5.8 WHO immunological classification HIV-infected children 0- 59 months (147)

WHO Immune Categorization	None or Not Significant	Mild Immune suppression	Advanced Immune suppression	Severe Immune suppression
< 11 months	CD4 >35%	CD4 30-35%	CD4 25-29%	CD4 <25% or CD4 count <1,500 cells/mm^3
12-35 months	CD4 >30%	CD4 25-30%	CD4 20-24%	CD4 <20% or CD4 count <750 cells/mm^3
36-59 months	CD4 >25%	CD4 20-25%	CD4 15-19%	CD4 <15% or CD4 count <350 cells/mm^3

5.15 Clinical history, Clinical findings, laboratory tests, acute phase reactants and poor clinical prognostic outcomes definitions used in this study

Clinical history: age, PCV and Hib vaccination

Clinical Findings: Severe Malnutrition, Fever, Hypoxia, Tachypnea, Crackles, Wheezing

Laboratory tests: HIV exposure status

Acute phase reactants: Raised CRP, Leucocytosis, Positive Antibiotic serum activity

Poor clinical prognostic outcomes: Prolonged hospitalization, Mechanical Ventilation, Death within 30 days hospitalization and presumed death

5.15.1 Clinical History

5.15.1.1 Age Categories

For the purposes of this study, due to the possible differences in pneumonia etiology and immune status by age, children were further grouped into three age categories: i.e.1-5 months (age category 1), 6-11 months (age category 2), and 12-59 months (age category 3).

5.15.1.2 Vaccine status (biologic status)

Vaccination status was defined based on the number of doses of PCV or HibCV a child received (as documented on the immunization record), and the child's age at first dose or age at vaccine introduction into the EPI in South Africa (for PCV), as follows:

Fully immunized for PCV was defined as:

- 3 or more doses; or
- 2 or more doses for a child aged 12 to 24 months at either first dose of vaccine or at vaccine introduction into the South African EPI
- 1 or more doses for a child aged 24 months or older at either first dose of vaccine or at vaccine introduction into the South African EPI
- PCV was first introduced into the South African EPI in July 2009, with no catch-up campaign, so the youngest PERCH cases who would have been eligible to have received three doses of PCV would have been 26 months of age at PERCH enrolment

Fully immunized for HibCV was defined as:

- 3 or more doses; or
- 1 or more doses for a child older than 12 months at first dose
- HibCV was first introduced into the South African EPI in 1999, so all PERCH cases were eligible to have received a full course of this vaccine

5.15.2 Clinical Findings

The clinical findings definitions used in the PERCH study were used in this study and are tabulated below; refer Table 5.9

Table 5.9 Standardized Clinical Findings Definitions used in this study

Clinical Parameters	**Definitions**
Severe Malnutrition	Weight-for-age less than -3 z-scores below the median of the WHO child growth standards (WHO Anthro, version 3.2.2, January 2011)
Fever	Axillary temperature ≥38 C on admission or clinical history of fever in the past 48 hours
Hypoxia	O_{2*} saturations < 90% on room air pulse-oximetry reading on admission or a child treated with supplemental oxygen on admission but without a room air pulse oximetry reading
Tachypnea	Age <2 months RR^ ≥60 bpm#; Age 2-11 months RR^ ≥50 bpm#; Age ≥12 months RR^ ≥40 bpm#
Crackles	Crackles heard on chest auscultation at admission either right or left side
Wheezing	Wheeze, non-responsive to a bronchodilator challenge, heard on chest auscultation at admission, either right or left side

*O_2 oxygen
^RR: respiratory rate
#bpm: breaths per minute

5.15.3 Acute phase reactants

The acute phase reactants definitions used in the PERCH study were used in this study, are tabulated below; refer Table 5.10 for detailed descriptions

Table 5.10 Standardized acute phase reactants definitions used in this study

Raised CRP*	CRP ≥40 mg/dL
Leucocytosis	For age categories 1 and 2: WCC ≥15 × 10^9/L For age category 3: WCC ≥13 × 10^9/L
Positive antibiotic serum activity	Positive if serum antibiotic activity zone of inhibition diameter > 6mm

*CRP: C-reactive protein

5.15.4 Poor clinical prognostic outcomes:

The poor clinical prognostic outcome definitions used in this study and are tabulated below; refer

Table 5.9 for detailed descriptions

Table 5.11 Poor clinical prognostic outcomes definitions

Mechanical Ventilation	Child treated with mechanical ventilation in intensive care units (as recorded on the ventilation status on admission and clinical follow-up case report forms); children who had ETT* specimens collected were also deemed to have been mechanically ventilated
Prolonged hospitalization	Length of hospitalization ≥ 3 days
Death within 30 days of hospitalization	Death within ≤ 30 days of discharge from hospital on follow up
Mechanical ventilation or death	Combined category of death within 30 days of hospitalization and the assumption if not mechanically ventilated then would have died

*ETT: endotracheal tube

5.16 Specific Pathogens Investigated in PERCH

Gastric aspirates (GA), endotracheal tube aspirates (ETT), lung aspirates (LA) and pleural fluid taps were obtained when clinically indicated. Induced sputum (IS) samples obtained routinely in PERCH cases in order to attribute pneumonia etiology had routine microscopy, culture and susceptibility testing, immunofluorescence for *P. jiroveci* and TB culture. Respiratory specimens i.e. NPOP swabs and IS were evaluated using the Fast-track Diagnostics Respiratory Pathogens 33 test (FTD Resp 33) (Fast-track Diagnostics, Sliema, Malta), a 33-target, eight-multiplex real-time PCR platform for the detection of the viruses, bacteria and fungal pathogens is listed below. Standard curves for quantification were generated using tenfold serial dilutions of plasmid standards provided by Fast-track Diagnostics on an approximately 3-monthly basis and were used to calculate pathogen density (copies/mL) from the sample cycle threshold (Ct) values. Real-time PCR was performed using an Applied Biosystems 7500® platform (Applied Biosystems, Foster City, CA).

Pathogens detected using the 33-plex RT-PCR included:

- **Bacterial pathogens:** *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*; *Streptococcus pneumonia*; *Haemophilus influenzae* type b; *Staphylococcus aureus*; *Moraxella catarrhalis*; *Bordetella pertussis*; *Klebsiella pneumoniae*; *Legionella* species; *Salmonella* species; and *Haemophilus influenzae* species other than type b.
- **Respiratory Viral pathogens:** influenza A, B and C; parainfluenza viruses 1, 2, 3 and 4; coronaviruses NL63, 229E, OC43 and HKU1; human metapneumoviruses A and B; human rhinovirus; respiratory syncytial viruses A and B; adenovirus; enterovirus; parechovirus; bocavirus; and human cytomegalovirus.
- **Fungal pathogen:** *Pneumocystis jiroveci*.

5.17 The PERCH Quantitative Analysis (PQA) Model

The PERCH Quantitative Analysis (PQA) model was developed as a "statistical probabilistic approach to incorporate data from a variety of specimens and tests from both cases and controls to produce an etiology pie for pneumonia. The PQA model is a partially latent class model (PLCM) analysis that extends the latent class approach to have a known latent state for some subjects, the controls that are known to have no pathogen infecting the lung" (148). "For cases diagnosed with pneumonia the pathogen infecting the lung was the target of interest. The analysis integrates data from multiple types of measurements, including both case-only and case-control measurements, and accounts for varying measurement error rates to estimate the distribution of pathogens among the cases. The proportion of cases with no identifiable pathogen was also estimated" (148, 149). The PQA model estimates the attributable probability of disease for each of the investigated pathogens, producing both a probability of attribution at an individual and population level (148, 149).

The PQA model, which is a PLCM takes into consideration the sensitivity and specificity of the tests used to identify respiratory pathogens in PERCH cases and controls using silver standard (eg., blood culture) and bronze standard (e.g., NPOP and IS) data and by comparing case pathogen prevalence against the prevalence of respiratory pathogens detected in the control NPOP specimens, factoring in seasonal changes in pathogen prevalence (148).

Dr Mahomed worked in person with the PERCH Core Team in particular Mr Z Wu, at the Johns Hopkins Bloomberg School of Public Health, in Baltimore, USA, on the South African specific PQA model. For the purposes of this analysis, the PQA model was programmed to perform 10,000 iterations on data from cases with interpretable chest X-rays using the R version 3.1.0 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). The model

generated a probability index for each of the 33 organisms (pathogen or pathogen combinations derived from Fast Track outputs and microbiologic testing) with the sum of the probability indices for the 33 pathogens adding to 1.0 for each individual patient. The PQA model "assumes there are no interactions between pathogens (i.e. conditional independence) and doesn't allow for synergistic co-infections with multiple pathogens. For each case a probability distribution of all pathogens is estimated, generating an etiologic histogram" (148, 149).

The PQA model was run by Dr Mahomed on 10 separate runs on separate days and the results were stable. Using the PQA model results, individual pathogens were grouped as bacteria, respiratory viral and *P. jiroveci*. Separate analyses was performed using a probability index of $\geq$ 0.5, $\geq$ 0.6 or $\geq$ 0.7 considered to be a positive probability for bacteria etiology and $\geq$ 0.5 considered to be a positive probability for respiratory viral and *P. jiroveci* etiology.

5.18 Microbiologically Confirmed Pneumococcal Pneumonia (MCPP)

All PERCH cases were evaluated for pneumococcus using blood culture, culture of IS and NPOP swabs. Microbiologically confirmed cases of pneumococcal pneumonia (MCCP) were assigned as being those with:

- Pneumococcus identified by culture of blood, pleural fluid or lung aspirate
- Fast-track PCR positive for *S. pneumoniae* on lung aspirate or pleural fluid samples; or
- Pneumococcal antigen in pleural fluid ie: Positive BinaxNOW (BinaxNOW *Streptococcus pneumoniae* Antigen Card, Alere, Orlando, Florida, USA).

5.19 *Pneumocystis jiroveci* testing

All respiratory specimens were tested for *P jiroveci* nucleic acid with the Fast Track PCR panel. Additionally, induced sputum, ETT, pleural fluid, and lung aspirate specimens were tested for *Pneumocystis* by immunofluorescence.

5.20 Pulmonary TB

5.20.1 Mycobacterium tuberculosis culture

Culture of sputum and gastric aspirate specimens for MTB was performed using liquid media at the TB Referral Laboratory of the National Health Laboratory Service (NHLS), Braamfontein, Johannesburg. Antimicrobial susceptibility testing was performed on all *M. tuberculosis* isolates. Non-tuberculous mycobacteria isolates were identified at the same TB Referral Laboratory.

5.20.2 Pulmonary TB

Clinically-diagnosed PTB was classified as children who did not have culture-confirmed disease, but who were elucidated to have been diagnosed with PTB during their hospitalisation as determined by:

- Having been started on TB treatment during the PERCH admission or;
- Having been notified with TB at the hospital-based PTB notification unit during their PERCH admission or;
- Having been discharged with the diagnosis of PTB (and not on TB treatment on admission)

5.20.3 Culture or clinical Pulmonary TB

For the purposes of this study we created a category culture or clinical PTB by combining culture confirmed PTB and clinically diagnosed PTB.

5.20.4 Non-TB Cases

Children who did not have culture-confirmed TB, and those not deemed to have clinically-diagnosed PTB as per the criteria stated above, were deemed to be ‘non-TB cases’.

5.21 Data analysis and statistics for objectives 2 to 5

Dr Mahomed accessed the clinical data through the PERCH database, managed by the EMMES Corporation (Maryland, USA). Microsoft excel was used for the detailed chest X-ray data. Statistical analyses were conducted by N. Mahomed using STATA, version 13.0 (StataCorp, College Station, Texas), assisted and verified by her supervisors and the PERCH Core Team (Ms C Prosperi and Ms M Higdon**)** from Johns Hopkins Bloomberg School of Public Health, Baltimore, USA, where Dr Mahomed spent time working on her PhD.

Descriptive statistics, e.g. median age in months with interquartile ranges, and comparison of medians were performed using the Wilcoxon rank sum test for non-parametric data. For this analysis a Bonferroni correction was done, with adjusted *p*-values <0.025 taken as statistically significant. HIV-infected and HEU children were compared with HIV-unexposed children as the reference group where applicable.

Statistical analysis of chest X-ray findings were restricted to cases with interpretable chest X-rays. Chest X-ray findings in HIV-infected and HEU children were compared with HIV-unexposed children as the reference group using a logistic regression model.

In order to determine the associations between chest X-ray patterns and clinical parameters and acute phase reactants, univariate comparisons were conducted including Pearson's chi-squared test and Fishers exact test (if the expected value in any of the cells in the generated two-by-two tables was less than five). Comparisons with two-sided *p*-values <0.2 in univariate analyses were incorporated into multivariate analyses, using stepwise logistic regression to determine the independent effects of variables potentially correlated to each other. This led to adjusting for age, HIV exposure status, nutritional status, hypoxia (low oxygen saturation), age-adjusted presence of tachypnea and presence of wheezing in the multiple logistic regression models.

A univariate logistic regression model was used for each HIV exposure group, to evaluate whether specific chest X-ray patterns were associated with pathogens identified on the PQA model; ie: bacterial based on a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7, respiratory viral based on a PQA model probability index ≥ 0.5 and *P. jiroveci* based on a PQA model probability index ≥ 0.5. This logistic regression model was also used to determine if specific chest X-ray patterns were associated with MCPP, culture confirmed PTB and culture or clinically confirmed PTB.

5.22 Ethics

The University of the Witwatersrand Human Research Ethics Committee (HREC) approved this study (clearance certificate M140421), refer Appendix 5. The PERCH study South African site was approved by the University of the Witwatersrand HREC (clearance certificate M10M101129), refer Appendix 6; and CHBAH Medical Advisory Board, refer Appendix 7. All children were assigned study numbers and data were analysed anonymously to ensure confidentiality. All participants' legal caregivers provided consent for inclusion in the PERCH, South Africa site.

5.23 Funding

Funding for this PhD study was provided by the Carnegie PhD Fellowship (Grant number: B8749.R01) and Discovery Foundation Academic Fellowship (Reference: 026555) awarded to Dr N Mahomed. The 7 country PERCH study was supported by The Bill & Melinda Gates Foundation (Grant number: 48968), awarded to the International Vaccine Access Centre, Department of International Health, Johns Hopkins Bloomberg School of Public Health.

6 Objective 1: Chest X-ray Quality Assurance in the 7 country PERCH Study: Results, Discussion, Limitations

Within the context of the PERCH 7 country study

Objective: To assess quality of chest X-rays in each of the 9 PERCH sites (in 7 countries) over a 14 month period by quantifying radiographic errors through use of a customized quality assessment form and to determine the impact of quality assurance activities on chest X-ray quality during the course of the chest X-ray quality assurance period in each of the 9 sites.

6.1 Results

6.1.1 Number of Chest X-rays with Quality Assurance Assessment in Each Site

A total of 747 chest X-rays in 9 sites (range of 44-119 per site) had quality assessment using the customized force choice reporting system; Table 6.1. In 8 out of the 9 sites quality assessment was performed on frontal chest X-rays only, and in Johannesburg quality assessment was performed in 81 (68%) frontal and 38 (32%) lateral chest X-rays. There was no statistically significant difference between the quality of frontal compared to lateral chest X-rays (p=0.274) in Johannesburg using the customized quality assessment.

In Johannesburg 811were performed and uploaded over the 14 month study period, hence 15% (119/811) had quality assessment. This percentage was considerably lower than Nakhon Phanom and Sa Keo sites where 72% (79/110) and 79% (44/56) of radiographs performed respectively, had quality assessment. This was due to the lower total number that were performed

and uploaded over the 14 month study period. The number of chest X-rays that had quality assessment for each of the 9 sites are summarised in table 6.1

Table 6.1 Number and percentage of Chest X-rays with Quality Assessment in Each Site

Site (Country)	**Total Number of CXRs that had quality assessment over 14 month period**	**Total number of CXRS loaded on EMMES Corporation, over 14 month study period**	**Percentage of CXRs that had quality assessment over 14 month study period**
Bamako	64	295	22%
Basse	90	455	20%
Dhaka	85	151	56%
Johannesburg	119	811	15%
Kilifi	70	297	24%
Lusaka	117	253	46%
Matlab	79	250	32%
Nakhon Phanom	79	110	72%
Sa Kaeo	44	56	79%

6.1.2 Chest X-Ray Quality Assessment in Each of the Six Parameters for Each Site

In all 9 sites a low percentage (0- 11%) of chest X-rays were reported as bad in the 5 parameters: positioning (1%), collimation (0-11%), exposure (0-7 %), inspiration (0-2 %) and processing (0-5%) using the customized chest X-ray reporting system. Motion was evident in 0-23% of chest X-rays.

Two out of the 9 sites ie: Dhaka and Kilifi scored above 80% for each of the 6 parameters assessed in the customized chest X-ray quality assessment. These 2 sites had the best chest X-rays quality assessment results. Refer Figures 6.1 to 6.6.

Three out of the 9 sites, Basse, Nakhon Phanom and Sa Kaeo scored above 80% for all parameters except collimation. In Basse 58% scored good, 39% scored fair and 3% scored bad for collimation. In Nakhon Phanom 51% scored good, 38% scored fair and 11% scored bad for collimation, while in Sa Kaeo 66% scored good, 27% scored fair and 7% scored bad for collimation using the customized chest X-ray quality assessment. Refer Figures 9.1 to 9.6.

Johannesburg scored 80% and above for all parameters assessed in the customized chest X-ray quality assessment except exposure. In Johannesburg 74% of chest X-rays were scored good quality, 22% scored fair and 4% as bad for exposure.

Bamako (Mali) scored 90% and above for 4 parameters: positioning, exposure, motion and inspiration. Bamako (Mali) scored 70% good, 25% fair and 5% bad for collimation and 51% good, 47% fair and 2% bad for processing using the customized chest X-ray quality assessment. Refer Figures 6.1 to 6.6.

Lusaka scored 80% above for 4 parameters positioning, motion, inspiration and processing. Lusaka scored 75% good, 24% fair and 1% bad for collimation and 59% good, 34% fair and 7% bad for exposure.

Matlab scored 80% and above for 3 parameters: positioning, collimation and inspiration. Matlab scored 50% good, 44% fair and 6% poor for exposure, 61% good, 34% fair and 5% bad for processing and 77% no motion and 23% motion. Refer Figures 6.1 to 6.6.

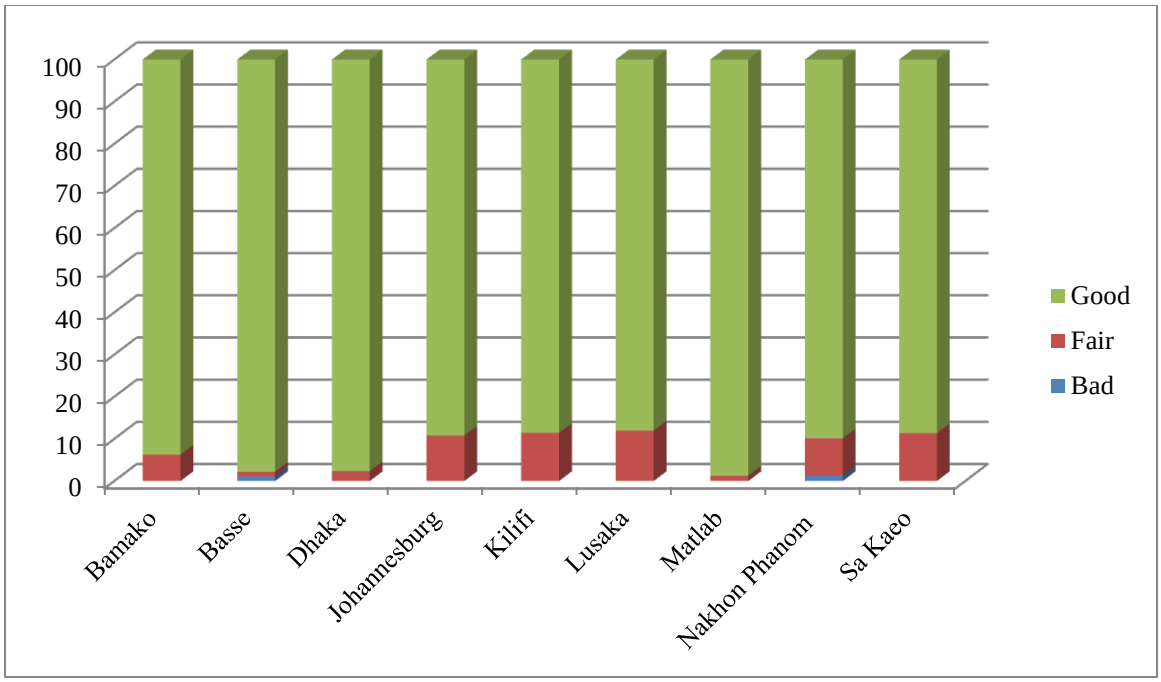

Figure 6.1: Bar Graph demonstrating **Positioning** results in each of the 9 sites

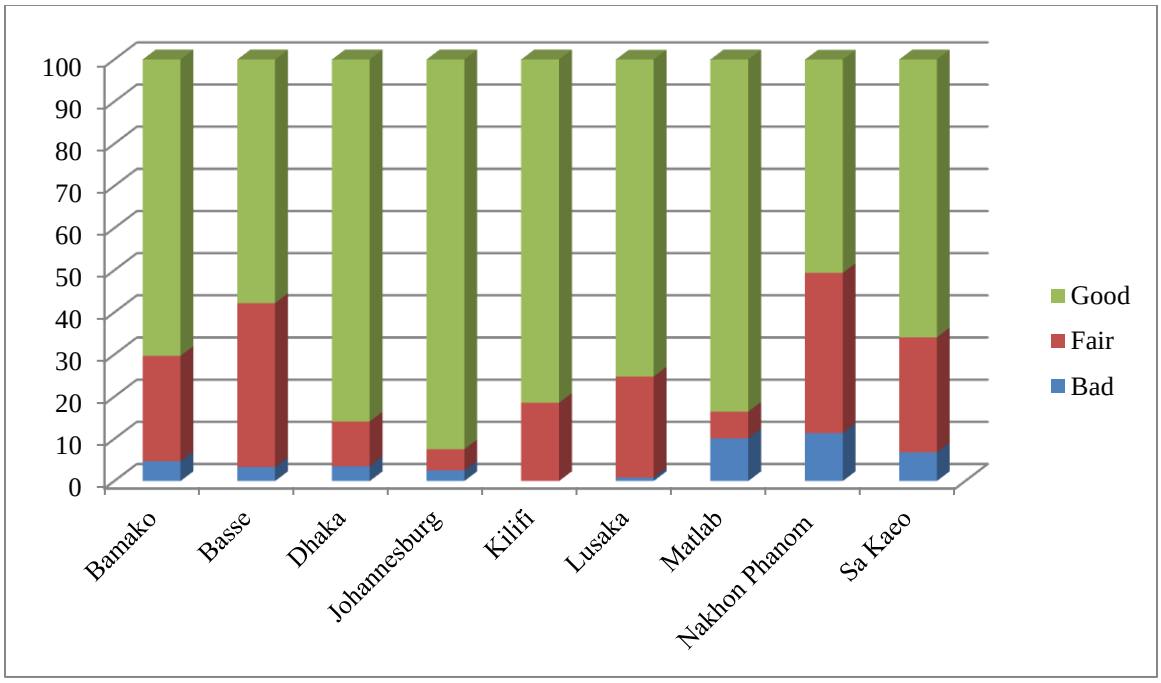

Figure 6.2: Bar Graph demonstrating **Collimation** results in each of the 9 sites

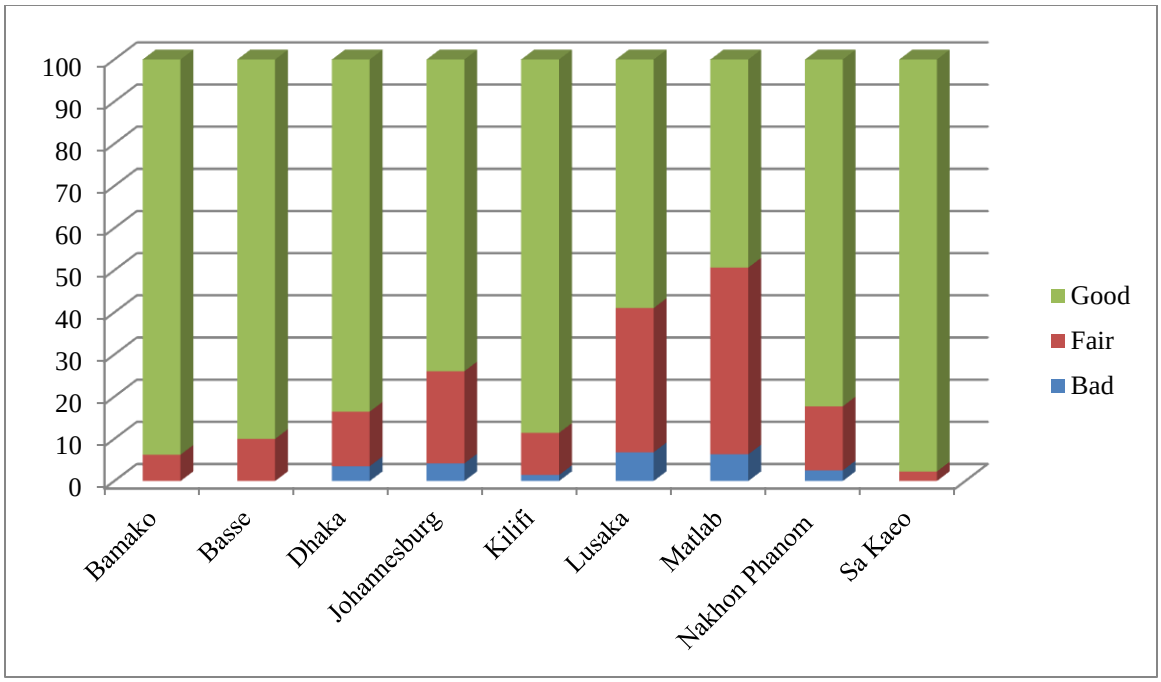

Figure 6.3: Bar Graph demonstrating **Exposure** results in each of the 9 sites

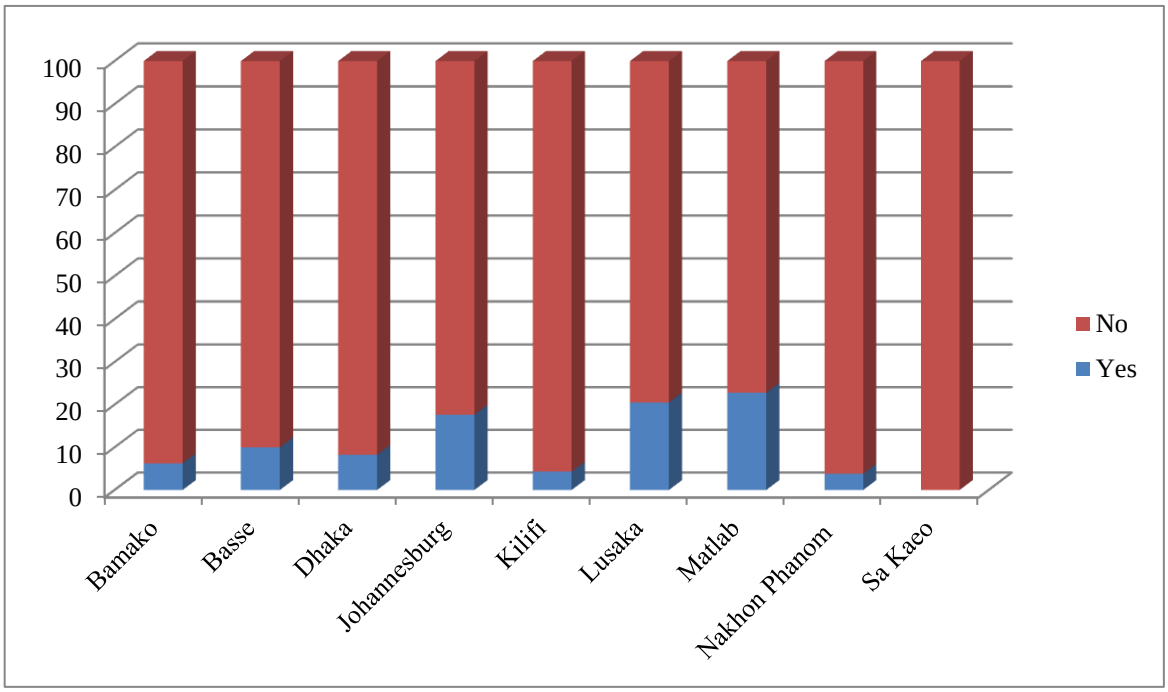

Figure 6.4: Bar Graph demonstrating **Motion** results in each of the 9 sites

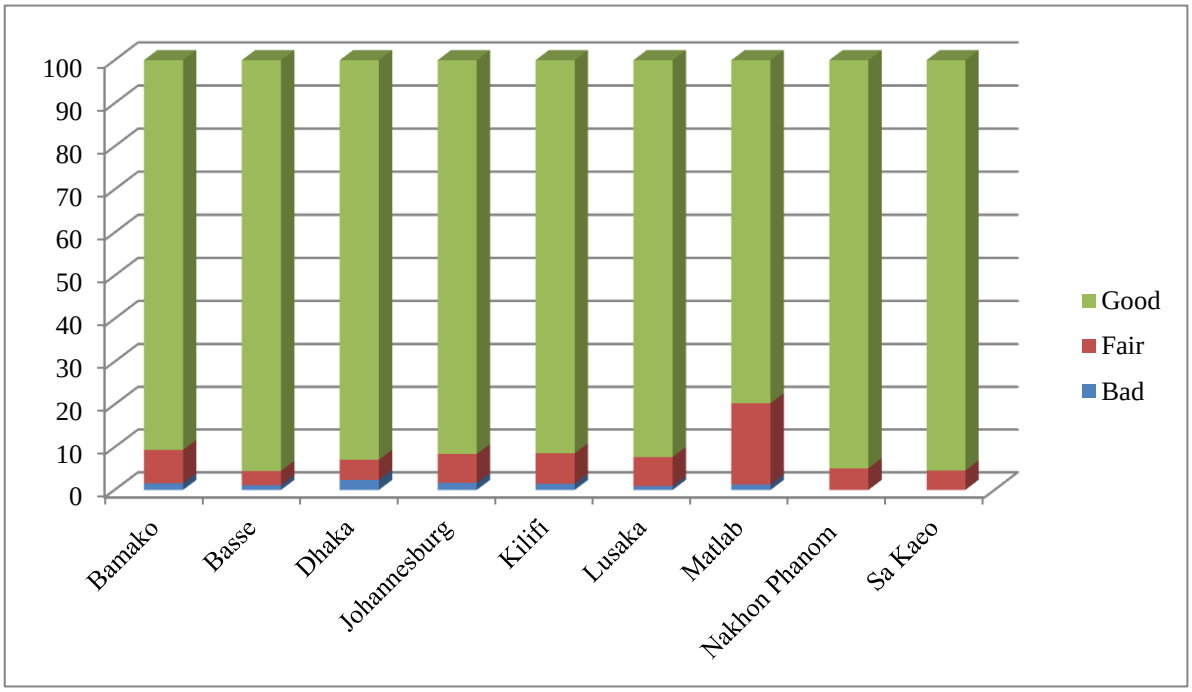

Figure 6.5: Bar Graph demonstrating **Inspiration** results in each of the 9 sites

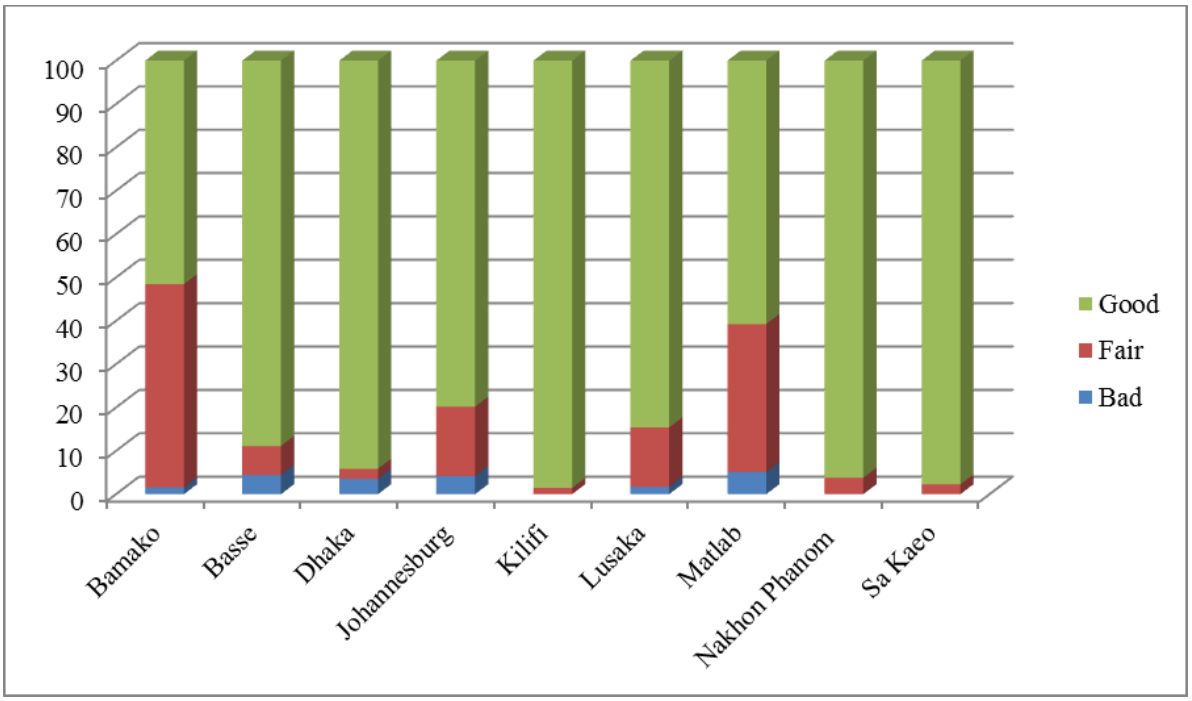

Figure 6.6: Bar Graph demonstrating **Processing** results in each of the 9 sites

6.1.3 Combined Nine Site Assessment

Combining the results of all 9 sites for each of the 6 chest X-ray quality assessment parameters; collimation was the worse scoring parameter with 20% assessed as fair and 4% as bad. Positioning and inspiration were the parameters that the sites performed best with 93% and 91% assessed as good respectively. Results are summarized in Table 6.2. A low percentage 0%-4% was assessed as bad making the chest X-ray uninterpretable. Twelve percent had motion.

Table 6.2 Combined Nine Site Results for each of the 6 Chest X-Ray Quality Assessment Parameters

Parameter	**Good N (%N)**	**Fair N (%N)**	**Bad N (%N)**
Positioning	691 (93)	54 (7)	2 (0.3)
Collimation	560 (75)	154 (21)	33 (4)
Exposure	578 (77)	145 (19)	24 (3)
Inspiration	684 (92)	54 (7)	9 (1)
Processing	623 (83)	105 (14)	19 (3)
Parameter	**No N (%N)**	**Yes N (%N)**	
Motion	658 (88)	89 (12)	

6.1.4 Chest X-ray Quality Time Series Analysis using Test for Trend

The test for trend analysis was performed for each of the 9 sites over the 14 month period using the scoring system described in the methods. Chest X-ray quality assurance activities made a significant impact in improving chest X-ray quality in 3 of the 9 sites over the 14 month period with a statistically significant improvement of chest X-ray quality for Matlab (p<0.001), Johannesburg (p=0.035), Nakhon Phanom (p<0.001). Refer Table 6.3 test for trend results. None of the 9 sites showed a statically significant worsening of chest X-ray quality over the 14 month period as determined by the test for trend analysis. The median quality assessment score out of a total of 11 for each month, per site is summarized in Table 6.3.

Table 6.3 Chest X-ray Quality Time Series Analysis over 14 month period for each of the 9 sites using Test for Trend

Site	**Median Quality Assessment Score out of a total of 11, for each site per Month**														***P* value**
	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***	
Bamako	10.5	N/A	N/A	11	9.5	9	N/A	10	N/A	N/A	10.5	10	N/A	N/A	0.426
Basse	10	10	11	10	11	9	N/A	11	N/A	N/A	10	N/A	N/A	11	0.089
Dhaka	11	11	10	10.5	11	10	11	11	11	9.5	N/A	10.5	11	11	0.659
Johannesburg	9.5	10.5	9	10	10	10	10	11	10.5	11	N/A	11	N/A	10	**0.035**
Kilifi	10.5	10	11	N/A	11	N/A	N/A	N/A	11	N/A	N/A	N/A	11	11	0.831
Lusaka	10	10	10	10.5	11	9	10	9	10	9	N/A	11	10	N/A	0.890
Matlab	9.5	6.5	8.5	9	N/A	9	N/A	8.5	9	10	N/A	10	11	11	**<0.001**
Nakhon Phanom	10	9.5	9	9.5	10	9	11	10.5	10	11	11	11	11	11	**<0.001**
Sa Kaeo	10.5	11	11	10	10.5	11	11	N/A	11	11	11	10	10	10.5	0.402
Combined 9 sites	10	10	10	10	11	9	10	10	10	10	10.5	11	11	11	**<0.001**

N/A – not applicable represents no chest X-Ray quality assessment for that month, due to no chest X-rays loaded for that month

6.2 Discussion: Objective 1

The chest X-ray is the most common imaging modality performed for clinical diagnosis of childhood pneumonia and remains the most accessible in paediatric radiology, especially in resource limited settings (14, 23, 29), despite advances in cross sectional thoracic imaging, like CT chest (150). The radiation dose from the chest X-ray is relatively low (0.02 mSv) (150). However the cumulative dose from multiple chest X-rays may be considerable (23). Radiographic errors in paediatric chest X-rays are highlighted because they contribute to increasing the difficulty in making a diagnosis, and are more likely to be unsatisfactory in paediatric patients due to incorrect exposure factors, poor positioning and poor immobilization (22, 151, 152). Such errors can result in an increased radiation dose due to the need for repeat imaging (22, 29).

In our results of chest X-ray quality assessment in children for diagnosis of pneumonia, collimation performed the worse of the 6 parameters, with 5 out of the 9 sites being graded sub-optimally for this. In this group of 5 sites 51%-75% were graded as good, 24%-39% as fair, 1%-11% as bad for collimation.

These findings are consistent with the findings by Hlabangana *et al* who conducted a chest X-ray quality assessment study on a total of 438 children over a 4 month period at a single hospital in South Africa with no paediatric trained radiographers (23), similar to the centres in the PERCH Study. The study was conducted using analogue chest X-rays (similar to Matlab, Lusaka and Nakhon Phanom. Twelve radiographic errors assessed were rotation (horizontal plane), kyphotic or lordotic views, poor collimation, parts cut-off, under-inspiration, scapula in the way, inability to visualize the central or peripheral vessels and the vessels behind the heart, inability to

visualize the tracheobronchial tree, presence of artefacts and absent or wrongly placed left or right markers. The most common error was poor collimation consistent the results of our study (23). This finding is further supported by Alt *et al* who found that paediatric chest X-ray collimation, patient centring and patient positioning was insufficient in both departments with or without paediatric competence (paediatric radiographers and radiologist) in children younger than 5 years (21).

The two sites with the best results Dhaka and Kilifi scored above 80% for all 6 parameters. While both sites have digital X-ray units, these sites do not have paediatric trained radiographers, the children are X-rayed in the same department as adults and Kilifi does not have an onsite radiologist. In Kilifi, radiographers have to routinely sign their name against all plain radiographs they perform. This may increase accountability when individual quality assessment feedback is given. In Dhaka site all PERCH chest X-rays were read for diagnostic and quality assurance purposes by the PERCH study clinicians and feedback on quality was given at regular intervals to the radiographers. These factors may have contributed to these 2 sites performing optimally.

Three of the 9 sites Matlab, Johannesburg and Nakhon Phanom showed a statistically significant improvement in chest X-ray quality over the 14 month period. Matlab used an analogue X-ray unit and scored sub-optimally for exposure, motion and processing. An important reason for improvement in chest X-ray quality would be improvement in processing as this site borrowed a better quality flatbed scanner (Epson 10000XL) from the Nakhon Phanom site, approximately 1 year into the study.

Johannesburg scored sub-optimally for exposure. This is consistent with the study by Gallet *et al* who assessed all plain radiographs performed in the department over a 5 year period for 13 quality assessment parameters (151). The authors found that overexposure to be the most common error in all radiographs. The Johannesburg site used 2 digital X-ray units in a paediatric radiology department. However dedicated and experienced radiographers were only allocated to the paediatric radiology department during working hours i.e.: Monday to Friday from 8am to 4 pm. After hours a larger pool of radiographers rotated through the paediatric radiology department, without experience in imaging of children. Feedback from the PERCH study chest X-ray quality assessments to the radiographers allocated to the paediatric radiology department and training of general radiographers by the radiographers allocated to paediatric radiology with experience in imaging of children could have accounted for the statistically significant improvement in chest X-ray quality in Johannesburg.

Nakhon Phanom scored sub optimally for collimation as clinician's routinely request babygrams or chest X-rays to include the abdomen for children presenting with clinical pneumonia. During the course of this study clinicians were educated on ALARA principles (26, 27) and the increased risk for radiation-induced cancer in children compared to adults (21, 22, 24). A modification in X-ray request forms from clinicians to only include the chest and avoid babygrams could have led to the statistically significant improvement in chest X-ray quality in this site. Another reason for the chest X-ray quality improvement is that this site converted from an analogue to a digital X-ray unit 6 months into the study.

In this study chest X-ray quality assurance intervention was applied in each of the 9 sites over the 14 month period (as described in Table 5.4) and none of the 9 sites showed a statistically significant worsening in chest X-ray quality over the 14 month period; Table 6.3. Hlabangana *et*

al showed statistically significant improvement (p=<0.0083) in the quality of chest X-rays in children under 5 years, immediately after a poster intervention. However this improvement was not sustained as they showed a statistically significant decline in quality of chest X-rays 2 months after the intervention (23). The authors demonstrated that short term interventions can assist in increasing awareness and in improving the quality of paediatric chest X-rays in an unsupervised unit but the improvement can only be sustained with regular and consistent quality assurance and quality improvement initiatives (23) as demonstrated in our study.

Matlab, Johannesburg and Lusaka had a significant number of chest X-rays scoring fair in exposure. A number of chest X-rays had motion in Matlab and Lusaka. To explain these radiographic errors it would be important to note that Matlab and Lusaka used analogue X-ray units, and could not pre-screen while performing the chest X-ray.

This study was performed in sick children, hospitalized for WHO-defined severe or very severe pneumonia, hence technical difficulties in obtaining chest X-rays in acutely ill children could have played a role in this study and has not been previously described in the literature. Furthermore unlike adult practice where a poor quality radiograph may be repeated, in paediatric practice a poor quality radiograph is often accepted, to avoid the increased dose to the patient from repeat exposures as emphasized by the ALARA principles (26, 27). In busy paediatric wards in resource limited settings it is often difficult to arrange for a repeat visit to the radiology department for children whose initial chest X-ray is of sub-optimal quality because of staff shortages or the clinical status of a paediatric patient and clinicians often forgo a repeat radiologic investigation in order to limit these inconveniences.

Matlab and Bamako had a significant number of chest X-rays scoring fair in processing. During the course of the study it was noted that digital X-ray unit in Bamako needed to be cleaned and serviced. A number of chest X-rays had linear lines suggestive of pressure marks from the processor. The delays in timely repair of the faulty equipment limited the quality of chest X-rays in Bamako. In Matlab the X-ray scanner machine did not have a transparency unit, which resulted in poor quality of chest X-rays that were scanned from analogue to digital format.

6.3 Study Limitations: Objective 1

Our study had a number of limitations. One external paediatric radiologist (Dr Manduka) reported chest X-ray quality through the customized report formatting; hence this study is unable to determine inter observer variability. However the strength of the study is that the same experienced external paediatric radiologist reported chest X-ray quality prospectively for each of the 9 sites over the course of the 14 month study period.

We were unable to evaluate the impact of the quality of chest X-rays in making a radiological diagnosis of CXR-PEP, other infiltrate or normal chest X-ray (15).

We were unable to analyse if specific clinical findings (eg: tachypnea, hypoxia) were predictive of poorer chest X-ray quality, due to limitations in the study design. Ten chest X-rays were randomly selected from each of the 9 sites every month for quality assessment in this study. Due to this randomization if children had both frontal and lateral chest X-rays as per Johannesburg, or multiple chest X-rays, chest X-rays from the same patient may have been randomly selected for chest X-ray quality assessment. While the date and time of the chest X-ray was performed and recorded, the exact date and time of the clinical findings were not always recorded, hence we were unable to analyse if specific clinical findings were predictive of poorer chest X-ray quality.

From the monthly uploads to the EMMES Corporation STATA software (StataCorp, College Station, Texas, USA), 3 of the 9 sites used analogue X-ray units and these sites scanned printed chest X-rays to a digital format, which could account for the disparity in chest X-ray quality in processing between the different sites.

A variable number of chest X-rays had quality assessment over the 14 month period in each of the 9 sites, due to the variable number of PERCH study chest X-rays that were performed and loaded on EMMES database monthly. Sites that performed a higher number of PERCH chest X-rays like Johannesburg tended to have a lower overall percentage of chest X-rays evaluated for quality assessment compared with sites that performed less PERCH study chest X-rays like the Thailand sites; and had a higher overall percentage that had chest X-ray quality assessment.

The site specific limitations and challenges in obtaining optimal chest X-ray quality are described in detail in Table 6.4.

Table 6.4: Site Specific Limitations and challenges in optimizing image quality

Site (Country)	**Radiology Department Site Limitations**
Bamako (Mali)	Faulty equipment required servicing and delays in timely repair limited quality of chest X-rays. For the first 6 months all PERCH chest X-rays were assessed weekly for diagnostic and quality assessment, this was changed to daily during the course of this study.
Basse (The Gambia)	Breakdown of the digital X-ray unit resulted in the use of back-up analogue X-ray unit with subsequent digitization of films. PERCH study site clinicians changed during study period, hence study clinicians had varying competencies in chest X-ray quality assessment. Reading of all chest X-rays for diagnostic and quality assessment done by study clinicians only commenced 4 months into the study.
Dhaka ICDDR-B (Bangladesh)	Plain film radiographs were not routinely read by a radiologist.

Dhaka Monowara (Bangladesh)	Private hospital where a broader pool of radiographers rotates without dedicated radiographers for paediatric imaging. PERCH chest X-ray quality assessments were not routinely directed to the radiographers at this site.
Johannesburg (South Africa)	Radiographers have a very high workload. Dedicated radiographers in paediatric radiology department available only during working hours ie: Monday to Friday 8am to 4 pm. PERCH feedback was only directed to radiographers in paediatric radiology department. A number of analogue portable CXRs performed on children due to significant distance of the radiology department from paediatric wards. Despite transitioning to a digital X-ray unit, CXRs had to be printed and scanned as no software to store CXRs digitally for 11 out of 14 month period.
Kilifi (Kenya)	Radiographers found positioning and imaging of very young children a challenge and did not have a patient immobilization device. This may have contributed to poorer positioning and collimation young children compared to other parameters.
Lusaka (Zambia)	Children are X-rayed in the same radiology department as adults and there are no radiographers dedicated to imaging of children. All chest X-rays that were performed in the paediatric campus were done with a portable analogue X-ray unit which may have impacted on chest X-ray quality especially with exposure and collimation. Dirty or damaged screens also led to artefacts like scratches on chest X-rays.
Matlab (Bangladesh)	One radiographer who performed X-rays on adults and children An analogue X-ray facility, with some limitations to maintained quality. The X-ray scanner machine did not have a transparency unit, a large flat bed scanner Epson 10000XL was borrowed from the Thailand site approximately 1 year into the study to improve CXR processing quality.
Nakhon Phanom (Thailand)	Clinicians routinely requested babygrams or chest X-rays to include the abdomen as part of routine clinical practice
Sa Kaeo (Thailand)	Clinicians routinely requested babygrams or chest X-rays to include the abdomen as part of routine clinical practice

6.4 Recommendations from this Study to Obtain Good Quality Chest X-rays with Dose Optimization in Developing Countries without Paediatric Radiographers and Paediatric Trained Radiologists

Quality assurance programs are paramount in radiology departments and do not need to be facilitated by radiologists, especially in resource limited settings. Having a core group of

radiographers trained and dedicated to radiographic imaging of children is very important especially in radiology departments where children are imaged with adults. Pairing radiographers with experience in imaging of children with less experienced radiographers is important to train junior staff in selecting optimal imaging parameters based on children's size. Ensuring proper positioning of the patient and immobilization techniques will optimize the quality of the radiograph and limit the radiation dose to children. Collimation is of concern and may be poor even in departments with paediatric trained radiographers. This is due to the use of wide collimation in moving, uncooperative children to prevent repeat imaging when the area of interest is outside the field of view (28).

Monthly random analysis of a set of radiographs with feedback to radiographers may be useful and can result in a sustained trend of improvement. Radiographers signing against each X-ray performed may improve accountability and allows for personalized feedback so that radiographers can improve on errors and prevent repeat imaging. Where possible, all radiographs should be reported by radiologists with real time feedback on quality to radiographers. Education of clinicians on the ALARA principles in children and Image Gently campaigns may enable optimization of request forms to prevent overexposure of children example babygrams. In addition, where possible stream lining workflow to avoid analogue portable X-rays, which have greater technical difficulty to perform especially for inexperienced radiographers.

Ensuring that all radiographic equipment is functioning optimally; with daily quality assurance routine checks. A medical physicist can choose the appropriate receptor, ensure adequate filtration and processing of images and optimize image quality (28).

7 Objective 2: Chest X-ray patterns by HIV-exposure Status: Results, Discussion, Limitations

Within the context of the PERCH study, South African site

To describe and compare chest X-ray patterns in HIV-unexposed, HIV- exposed-uninfected (HEU) and HIV-infected children 28 days to 59 months of age hospitalized with WHO-defined severe or very severe community acquired pneumonia, and to determine the association between HIV-exposure status and chest X-ray patterns

7.1 Results

7.1.1 Interpretable Chest X-rays

During the two year study period 920 cases with WHO-defined clinical severe or very severe pneumonia and 964 healthy community controls were enrolled. Frontal chest X-rays were available in 885 (96%) cases. Of the 885 children with available chest X-rays, 27 (3%) were uninterpretable based on the 3 reader consensus reading. Refer Figure 7.1. Of the remaining 858 children with frontal chest X-rays, 501 (58%) also had lateral chest X-rays.

7.1.2 Demographic Data

The median age was 6 months (interquartile range, 2 to 12 months), with a mean age 9.04 months. Of the 858 children with interpretable chest X-rays 426 (50%) were 1 to 5 months of age (age category 1), 212 (24%) were 6 to 11 months of age (age category 2) and 220 (26%) between 12 and 59 months of age (age category 3).

The HIV status of the 858 children included 245 (29%) HIV-unexposed, 284 (33%) HEU, and 108 (13%) being HIV-infected. Furthermore, 183 (21%) were presumed to be HIV-unexposed based on the child being ≥7 months of age with a negative HIV-ELISA test, not being on antiretroviral treatment and the mother reported she was HIV negative (albeit no documentation

thereof). Children were categorised as HIV Unknown Exposure, Uninfected in 38 (4%) of cases. Refer Figure 7.1.

There were no significant differences in the chest X-ray features between the presumed HIV-unexposed and HIV-unexposed children for the main chest X-ray findings including air space disease, CXR-PEP , other infiltrate only , chronic lung disease , bilateral air trapping , intrathoracic lymphadenopathy, cardiomegaly and normal chest X-ray (p>0.05 for all comparisons). As such we combined these two groups under the HIV-unexposed category (n= 428; 50% of all cases).

In summary chest X-rays were available in 885 (96%) cases. Of these 27 (3%) were uninterpretable based on the 3 reader consensus reading. From the 858 children with interpretable chest X-rays, 428 (50%) were HIV-unexposed, 284 (33%) were HEU, 108 (13%) HIV-infected and 38 (4%) HIV-unknown exposure, uninfected.

Of the 108 HIV-infected children, CD4 results were available in 106 (98%) of children. Using the WHO immune categorization; refer Table 5.8 in methods chapter (147), 3 (3%) of children had no immune suppression, 9 (8%) had mild immune suppression, 7 (7%) advanced immune suppression and 87 (82%) had severe immune suppression. Thirty one (29%) of HIV-infected children were on anti-retroviral therapy prior to being hospitalized for WHO-defined severe or very severe pneumonia.

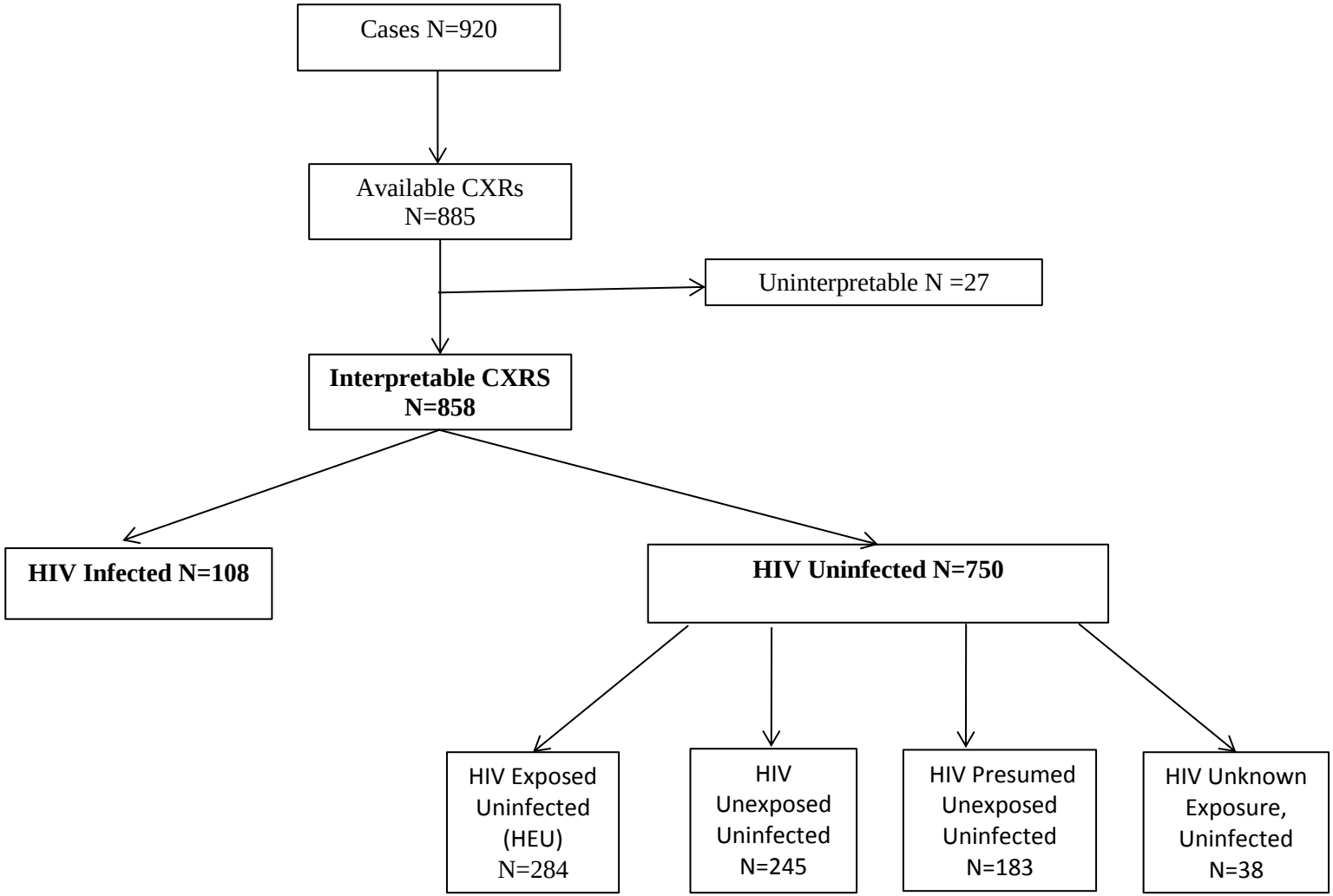

Figure 7.1 Availability of chest X-rays in children 1-59 months hospitalised for WHO-defined severe or very severe pneumonia and associated HIV-exposure and infection status

7.1.3 Chest X-Ray Findings in Children Hospitalized for WHO-defined Severe or very Severe Pneumonia, Stratified by HIV Status

During the two year study period 920 cases with WHO-defined clinical severe or very severe pneumonia were enrolled. Chest X-rays were available in 885 (96%) cases. Of these 27 (3%) were uninterpretable based on the 3 reader consensus reading. From the 858 children with interpretable chest X-rays, 428 (50%) were HIV-unexposed, 284 (33%) were HEU, 108 (13%) HIV-infected and 38 (4%) HIV-unknown exposure, uninfected.

The most common chest X-ray finding in all children hospitalized with WHO-defined severe or very severe pneumonia, analysed by HIV-exposure status, was CXR-PEP. This was prevalent among 38% HIV-unexposed, 33% HEU and 60% of HIV-infected children, with most of these cases due to airspace disease and only 2-7% due to pleural effusion; Table 7.1. There was no significant difference between HEU and HIV-unexposed children for any of the detailed chest X-ray patterns under air space disease or for CXR-PEP; Table 7.1.

CXR-PEP was twice as common in HIV-infected children (OR 2.5; 95% CI 1.6-3.8) compared with HIV-unexposed children. Under the chest X-ray category of air space disease; lobar consolidation was the most common finding in all 3 groups, and was 1.6 fold (95% CI 1.0-2.5) more common in HIV-infected children (31%) compared to HIV-unexposed children (22%), as was multi-lobar consolidation (17% vs. 8%; OR 2.2; 95% CI 1.2-4.0) and segmental/sub segmental consolidation (14% vs 7%, OR 2.0; 95% CI 1.1-3.8); respectively; Table 7.1.

Other infiltrate (with or without presence of CXR-PEP) was similar between HIV-unexposed children (31%) and HEU children (36%); but 2.4-fold (95% CI 1.5-3.6) more common in HIV-infected children (51%) than HIV-unexposed children. The most common patterns of other

infiltrate was reticular pattern, which was also more common in HIV-infected children (28%) compared with HIV-unexposed children (18%; OR 1.7; 95% CI 1.1-2.9). Similarly miliary infiltrate was 2.4 fold (95% CI 1.2-4.8) more common in HIV-infected (13%) compared with HIV-unexposed children (6%).

Other types of other infiltrates evident on chest X-ray which were not significantly different by HIV exposure status included presence of ground glass infiltrate (3-6%), peri-bronchial thickening (6-10%), reticular-nodular infiltrate (3-6%), large nodular infiltrate (1-3%) and peri-hilar streakiness (5-7%) which was uncommon in all 3 HIV exposure groups; with no significant difference between HIV-infected compared to HIV-unexposed children, or HEU compared to HIV-unexposed children.

Volume loss/lung collapse was similar across the 3 HIV-exposure groups (9-11%). Lung expansion/bulging fissure was found in 1%, while lung abscess was not found. Pleural disease was uncommon across the 3 HIV-exposure groups (2-7%), all of which were due to pleural effusion; and was 3.7 fold (95% CI 1 .4-9.9) more common in HIV-infected children (7%) compared to HIV-unexposed children (2%); refer Table 7.1.

Radiographic evidence of chronic lung disease (1-5%) was uncommon in all 3 HIV-exposure groups. However, under chronic lung disease bronchiectasis was 5.4- fold (95% CI 1.2-24.7) more prevalent in HIV-infected children (4%) compared to HIV-unexposed children (1%). In all 3 HIV groups presence of lung parenchymal cavitation was prevalent in 1% of cases; Table 7.1.

Intrathoracic lymphadenopathy was prevalent in 14-17% of children with no significant difference between HIV-infected compared to HIV-unexposed, or HEU and HIV-unexposed

children. The most common pattern of intrathoracic lymphadenopathy was the doughnut sign (13-14%), followed by hilar mediastinal masses (5-8%), whilst tracheal/bronchial compression (3%), unilateral air trapping (1%), lobar collapse (0-1%) and hilar elevation (0%) were uncommon.

Other radiological features which did not differ by HIV exposure status included bilateral air trapping (14-19%) and cardiomegaly (4-5%). Furthermore, the chest X-ray was 5.8-fold (95% CI 2.6-12.9) more likely to be categorized as being normal among HIV-unexposed children (29%) compared to HIV-infected children (6%; p= 0.000); Table 7.1. There was no difference for presence of a normal chest X-ray between HIV-unexposed compared with HEU children (29%). Refer Table 7.1

Table 7.1 Chest X-ray findings in Children hospitalized for WHO-defined severe or very severe pneumonia stratified by HIV Status

Chest X-ray Pattern	**HIV-infected N=108 (%)**	**HEU N=284 (%)**	**HIV-unexposed N=428 (%)**	**HIV-infected vs HIV-unexposed OR (95% CI)**	**HEU vs HIV-unexposed OR (95% CI)**
Airspace disease	**65 (60)**	**91 (32)**	**163 (38)**	**2.5 (1.6-3.8)**	**0.8 (0.6-1.1)**
Segmental/sub segmental consolidation	15 (14)	16 (6)	32 (7)	2.0 (1.1-3.8)	0.7 (0.4-1.4)
Lobar consolidation	34 (31)	46 (16)	96 (22)	1.6 (1.0-2.5)	0.7 (0.5-1.1)
Multi-lobar consolidation	18 (17)	31 (11)	36 (8)	2.2 (1.2-4.0)	1.3 (0.8-2.2)
Volume loss/lung collapse	12 (11)	26 (9)	48 (11)	1.0 (0.5-1.9)	0.8 (0.5-1.3)
Expansion/bulging fissure	0 (0)	0 (0)	1 (1)	1.0	1.0
Lung abscess	0 (0)	0 (0)	0 (0)	-	-
Pleural disease	8 (7)	9 (3)	9 (2)	**3.7 (1.4-9.9)**	**1.5 (0.6-3.9)**
Pneumothorax	1 (1)	2 (1)	2 (1)	2.0 (0.2-22.2)	1.5 (0.2-10.8)
Pleural effusion	7 (7)	7 (3)	7 (2)	4.2 (1.4-12.2)	1.5 (0.5-4.4)
Pleural plaques/calcification	0 (0)	0 (0)	0 (0)	-	-
CXR-PEP*	**65 (60)**	**94 (33)**	**163 (38)**	**2.5 (1.6-3.8)**	**0.8 (0.6-1.1)**

Other infiltrate#	55 (51)	103 (36)	131 (31)	**2.4 (1.5-3.6)**	**1.3 (0.9-1.7)**
Peribronchial thickening	11 (10)	17 (6)	29 (7)	1.6 (0.8-3.2)	0.9 (0.5-1.6)
Reticulo-nodular infiltrate	6 (6)	10 (4)	12 (3)	2.0 (0.7-5.6)	1.2 (0.5-3.0)
Reticular infiltrate	30 (28)	60 (21)	77 (18)	1.7 (1.1-2.9)	1.2 (0.8-1.8)
Millary infiltrate (nodules < 2mm)	14 (13)	17 (6)	25 (6)	2.4 (1.2-4.8)	1.0 (0.5-1.9)
Large nodular infiltrate (nodules > 2mm)	3 (3)	1 (1)	4 (1)	3.0 (0.7-13.7)	0.4 (0-3.4)
Perihilar streakiness	8 (7)	21 (7)	21 (5)	1.6 (0.7-3.6)	1.5 (0.8-2.9)
Ground glass infiltrate	6 (6)	15 (5)	13 (3)	1.9 (0.7-5.1)	1.8 (0.8-3.8)
Other infiltrate only~	**29 (27)**	**77 (27)**	**88 (21)**	**1.4 (0.9-2.3)**	**1.4 (1.0-2.0)**
Chronic lung disease	**5 (5)**	**4 (1)**	**5 (1)**	**4.1 (1.2-14.5)**	**1.2 (0.3-4.5)**
Fibroses	0 (0)	0 (0)	0 (0)	-	-
Bronchiectasis	4 (4)	3 (1)	3 (1)	5.4 (1.2-24.7)	1.5 (0.3-7.5)
Cavities	1 (1)	1 (1)	2 (1)	2.0 (0.2-22.2)	0.8 (0.1-8.3)

Intrathoracic lymphadenopathy	**18 (17)**	**41 (14)**	**68 (16)**	**1.1 (0.6-1.9)**	**0.9 (0.6-1.4)**
Hilar or mediastinal masses	5 (5)	18 (6)	34 (8)	0.6 (0.2-1.5)	0.8 (0.4-1.4)
Hilar elevation	0 (0)	0 (0)	0 (0)	-	-
Mediastinal shift	0 (0)	0 (0)	0 (0)	-	-
Tracheal or bronchial compression	3 (3)	8 (3)	12 (3)	1.0 (0.3-3.6)	1.0 (0.4-2.5)
Unilateral air-trapping	1 (1)	2 (1)	3 (1)	1.3 (0.1-12.9)	1.0 (0.2-6.1)
Lobar collapses	1 (1)	0 (0)	2 (1)	2.0 (0.2-22.1)	1.0
Doughnut sign	15 (14)	36 (13)	60 (14)	1.0 (0.5-1.8)	0.9 (0.6-1.4)
Bilateral air trapping	**21 (19)**	**42 (15)**	**60 (14)**	**1.5 (0.9-2.7)**	**1.1 (0.7-1.6)**
Cardiomegaly	**6 (6)**	**15 (5)**	**18 (4)**	**1.3 (0.5-3.5)**	**1.3 (0.6-2.6)**
Normal^	**7 (6)**	**81 (29)**	**123 (29)**	**5.8 (2.6-12.9)**	**1.0 (0.7-1.4)**

* Airspace disease and/or pleural disease, may include other infiltrate only
# Other infiltrate may or may not include CXR-PEP
~ Other infiltrate without CXR-PEP
^ Absence of airspace disease, pleural disease, other infiltrate, chronic lung disease, intrathoracic lymphadenopathy and bilateral air trapping

7.1.4 Chest X-ray findings in Children Hospitalized for WHO-defined severe or very severe pneumonia, Stratified by Age Category and HIV status

Due to the possible differences in pneumonia etiology and immune status by age, the interpretation of chest X-rays were further stratified into age categories 1 to 5 months, 6 to 11 months and 12 to 59 months and by HIV exposure status; Tables 7.2, 7.3 and 7.4 respectively.

7.1.4.1 Chest X-ray findings in Infants 1-5 months, Hospitalized for WHO-defined severe or very severe pneumonia, Stratified by HIV status

In infants 1-5 months of age the commonest chest X-ray finding, analysed by HIV-exposure status, was CXR-PEP prevalent among 40% HIV-unexposed, 30% HEU and 59% of HIV-infected children, with most of these cases due to air space disease and only 1-2% due to pleural effusion. CXR-PEP was twice as common in HIV-infected infants (OR 2.1; 95% CI 1.1-4.1) compared with HIV-unexposed infants; Table 7.2.

Under air space disease multi-lobar consolidation was more common (OR 2.5; 95% CI 1.1-6.1) in HIV-infected (20%) compared with HIV-unexposed infants (9%). Conversely lobar consolidation was 50% less likely (95% CI 0.3-0.9) in HEU (15%) compared with HIV-unexposed infants (25%). Pleural disease was uncommon across the 3 HIV groups (2%), with no significant differences between HIV-unexposed and HIV-infected or HEU infants.

Other infiltrate (with or without presence of CXR-PEP) was similar between HIV-unexposed (27%) and HEU infants (34%), but 1.9 fold (95% CI 1.0-3.7) more common (in HIV-infected (41%) than HIV-unexposed infants. The most common patterns of other infiltrate were reticular pattern (16-20%) in all three HIV groups. Also, there were no differences in the prevalence of a

other infiltrate in the absence of CXR-PEP between HIV-unexposed and HIV-infected or HEU infants; refer Table 7.2.

Bilateral air trapping was 3.3-fold (95% CI 1.6-7.1) more common in HIV-infected infants (30%), compared with HIV-unexposed infants (12%), whilst there was no difference in prevalence of chest X-ray features such as chronic lung disease (1-2%), intrathoracic lymphadenopathy (9-11%) and cardiomegaly (2-7%). The chest X-rays were, however, 3.9-fold (95% CI 1.4-10.4) more likely to be categorized as being normal among HIV-unexposed children (34%) compared to HIV-infected children (11%), but the frequency thereof was similar when comparing HIV-unexposed to HEU children (32%); Table 7.2.

7.1.4.2 Chest X-ray findings in children 6-11 months, Hospitalized for WHO-defined severe or very severe pneumonia, Stratified by HIV status

In children 6-11 months of age the most common chest X-ray finding was CXR-PEP, prevalent among 39% HIV-unexposed, 37% HEU and 65% of HIV-infected children, with most of these cases due to airspace disease. Pleural effusion was prevalent in only 2-10% of children. CXR-PEP was 2.8-fold (95% CI 1.2-6.4) more common in HIV-infected compared with HIV-unexposed children. Lobar consolidation was 3.7 fold more common (95% CI 1.6-8.7) in HIV-infected children (45%) compared with HIV-unexposed children (18%); Table 7.3.

Other infiltrate (with or without presence of CXR-PEP) was 3.1-fold (95% CI 1.3-7.2) more common in HIV-infected children (61%) compared with HIV-unexposed children (34%). Under other infiltrate the significant finding was reticular infiltrate, which was 2.4-fold (95% CI 1.0-5.5) more common in HIV-infected children (39%) compared with HIV-unexposed (21%) children. Furthermore, peri-bronchial thickening was also 3.8 fold (95% CI 1.1-14.1) more common in HIV-infected children (16%) compared with HIV-unexposed children (5%).

Chest X-ray findings which did not differ by HIV group status included presence of intra-thoracic lymphadenopathy (16-19%), bilateral air trapping (13-16%) and cardiomegaly (4-6%). The chest X-ray were, however, 8.5-fold (95% CI: 1.1-67.5) more likely to be categorized as normal in HIV-unexposed (24%) compared to HIV-infected children (3%); generally the chest X-ray findings were similar between HIV-unexposed compared with HEU (22%) children in this age category for normal chest X-ray; Table 7.3.

7.1.4.3 Chest X-ray findings in children 12-59 months, Hospitalized for WHO-defined severe or very severe pneumonia, Stratified by HIV status

In children 12-59 months of age, the most common chest X-ray finding was CXR-PEP, prevalent among 34% HIV-unexposed, 32% HEU and 58% of HIV-infected children, most of which was due to airspace disease. CXR-PEP was 2.7-fold (95% CI 1.2-6.1) more common in HIV-infected compared with HIV-unexposed children, including segmental/sub segmental consolidation which was 4.0-fold (95% CI 1.3-12.1) more common in HIV-infected children (23% vs. 7%) compared with HIV-unexposed children. Similarly, pleural disease was 5.7-fold (95% CI 1.2-26.9) more common in HIV-infected children (13%) than HIV-unexposed children (3%); Table 7.4.

Other infiltrate was also 2.3-fold (95% CI 1.0-5.1) more common in HIV-infected children (55%) than HIV-unexposed (35%) children, with miliary infiltrate being 3.5-fold (95% CI 1.2-10.4) more common in HIV-infected children (23% vs 8%) compared with HIV-unexposed children; Table 7.4.

Furthermore, chronic lung disease was 8.6-fold (95% CI 1.5-49.3) more common in HIV-infected children (13%) than HIV-unexposed children (2%), whilst there were no differences in

prevalence of intra-thoracic lymphadenopathy (18-29%), bilateral air trapping (10-16%) and cardiomegaly (3-10%) between the 3 HIV-exposure groups.

HIV-unexposed children were 11.1-fold (95% CI 1.4-87.7) more likely to have a normal chest X-ray (25%) compared to HIV-infected children (3%). Similar to other age-groups, there was no difference in the chest X-ray features between HIV-unexposed children compared with HEU children for normal chest X-ray; Table 7.4.

Table 7.2 Chest X-ray findings in Infants 1-5 months (age category 1) hospitalized for WHO-defined severe or very severe pneumonia, stratified by HIV status

Chest X-ray Pattern	**HIV-infected N=46 (%)**	**HEU N=153 (%)**	**HIV-unexposed N=206 (%)**	**HIV-infected vs HIV-unexposed OR (95% CI)**	**HEU vs HIV-unexposed OR (95% CI)**
Airspace disease	**27 (59)**	**46 (30)**	**82 (40)**	**2.1 (1.1-4.1)**	**0.7 (0.4-1.1)**
Segmental/sub segmental consolidation	6 (13)	6 (4)	15 (7)	1.91 (0.7-5.2)	0.5 (0.2-1.4)
Lobar consolidation	12 (26)	23 (15)	52 (25)	1.1 (0.5-2.2)	0.5 (0.3-0.9)
Multi-lobar consolidation	9 (20)	18 (12)	18 (9)	2.5 (1.1-6.1)	1.4 (0.7-2.8)
Volume loss/lung collapse	2 (4)	10 (7)	21 (10)	0.4 (0.1-1.8)	0.6 (0.3-1.3)
Expansion/bulging fissure	0 (0)	0 (0)	1 (1)	1.0	1.0
Lung abscess	0 (0)	0 (0)	0 (0)	-	-
Pleural Disease	**1 (2)**	**3 (2)**	**4 (2)**	**1.1 (0.1-10.2)**	**1.0 (0.2-4.6)**
Pneumothorax	0 (0)	2 (1)	2 (1)	1.0	1.4 (0.2-9.7)
Pleural effusion	1 (2)	1 (1)	2 (1)	2.3 (0.2-25.5)	0.7 (0.1-7.5)
Pleural plaques/calcification	0 (0)	0 (0)	0 (0)	-	-
CXR-PEP*	**27 (59)**	**49 (32)**	**82 (40)**	**2.1 (1.1-4.1)**	**0.7 (0.5-1.1)**

Other Infiltrate#	**19 (41)**	**52 (34)**	**55 (27)**	**1.9 (1.0-3.7)**	**1.4 (0.9-2.2)**
Peribronchial thickening	5 (11)	6 (4)	11 (5)	2.2 (0.7-6.6)	0.7 (0.3-2.0)
Reticulo-nodular infiltrate	2 (4)	3 (2)	4 (2)	2.3 (0.4-12.9)	1.0 (0.2-4.6)
Reticular infiltrate	9 (20)	28 (18)	32 (16)	1.3 (0.6-3.0)	1.2 (0.7-2.1)
Miliary infiltrate (nodules < 2mm)	3 (7)	8 (5)	8 (4)	1.7 (0.4-6.8)	1.4 (0.5-3.7)
Large nodular infiltrate (nodules > 2mm)	1 (2)	1 (1)	2 (1)	2.3 (0.2-25.5)	0.7 (0.1-7.5)
Perihilar streakiness	4 (9)	10 (7)	8 (4)	2.4 (0.7-8.2)	1.7 (0.7-4.5)
Ground glass infiltrate	4 (9)	11 (7)	9 (4)	2.1 (0.6-7.1)	1.7 (0.7-4.2)
Other infiltrate only~	**10 (22)**	**39 (25)**	**37 (18)**	**1.3 (0.6-2.8)**	**1.6 (0.9-2.6)**
Chronic Lung	**1 (2)**	**2 (1)**	**2 (1)**	**2.3 (0.2-25.5)**	**1.4 (0.2-9.7)**
Fibroses	0 (0)	0 (0)	0 (0)	-	-
Bronchiectasis	0 (0)	1 (1)	2 (1)	1.0	0.7 (0.1-7.5)
Cavities	1 (2)	1 (1)	0 (0)	3.3 (0.2-55.1)	1.0

Intrathoracic Lymphadenopathy	**4 (9)**	**17 (11)**	**19 (9)**	**0.9 (0.3-2.9)**	**1.2 (0.6-2.5)**
Hilar or mediastinal masses	1 (2)	7 (5)	9 (4)	0.5 (0.1-3.9)	1.0 (0.4-2.9)
Hilar elevation	0 (0)	0 (0)	0 (0)	-	-
Mediastinal shift	0 (0)	0 (0)	0 (0)	-	-
Tracheal or bronchial compression	0 (0)	3 (2)	7 (3)	1.0	0.6 (0.1-2.2)
Unilateral air-trapping	0 (0)	2 (1)	2 (1)	1.0	1.4 (0.2-9.7)
Lobar collapses	0 (0)	0 (0)	1 (1)	1.0	1.0
Doughnut sign	4 (9)	13 (9)	15 (7)	1.2 (0.4-3.8)	1.2 (0.5-2.6)
Bilateral air trapping	**14 (30)**	**21 (14)**	**24 (12)**	**3.3 (1.6-7.1)**	**1.2 (0.6-2.3)**
Cardiomegaly	**1 (2)**	**10 (7)**	**10 (5)**	**0.4 (0.1-3.5)**	**1.4 (0.6-3.4)**
Normal^	5 (11)	49 (32)	69 (34)	**3.9 (1.4-10.4)**	**0.9 (0.6-1.9)**

*Airspace disease and/or pleural disease, may include other infiltrate only
Other infiltrate may or may not include CXR-PEP
~ Other infiltrate without CXR-PEP
^ Absence of airspace disease, pleural disease, other infiltrate, chronic lung disease, intrathoracic lymphadenopathy and bilateral air trapping

Table 7.3 Chest X-ray findings in Children 6-11 months (age category 2) hospitalized for WHO-defined severe or very severe pneumonia, stratified by HIV status

Chest X-ray Pattern	**HIV-infected N=31(%)**	**HEU N=68 (%)**	**HIV-unexposed N= 104 (%)**	**HIV-infected vs HIV-unexposed OR (95% CI)**	**HEU vs HIV-unexposed OR (95% CI)**
Airspace disease	**20 (65)**	**25 (37)**	**41 (39)**	**2.8 (1.2-6.4)**	**0.9 (0.5-1.7)**
Segmental/sub segmental consolidation	2 (6)	7 (10)	9 (9)	0.7 (0.1-3.6)	1.2 (0.4-3.4)
Lobar consolidation	14 (45)	13 (19)	19 (18)	3.7 (1.6-8.7)	1.1 (0.5-2.3)
Multi-lobar consolidation	5 (16)	5 (7)	12 (12)	1.5 (0.5-4.6)	0.6 (0.2-1.8)
Volume loss/lung collapse	7 (23)	8 (12)	13 (13)	2.0 (0.7-5.7)	0.9 (0.4-2.4)
Expansion/bulging fissure	0 (0)	0 (0)	0 (0)	-	-
Lung abscess	0 (0)	0 (0)	0 (0)	-	-
Pleural Disease	**3 (10)**	**2 (3)**	**2 (2)**	**5.5 (0.9-34.3)**	**1.5 (0.2-11.2)**
Pneumothorax	0 (0)	0 (0)	0 (0)	-	-
Pleural effusion	3 (10)	2 (3)	2 (2)	5.5 (0.9-34.3)	1.5 (0.2-11.2)
Pleural plaques/calcification	0 (0)	0 (0)	0 (0)	-	-
CXR-PEP*	**20 (65)**	**25 (37)**	**41 (39)**	**2.8 (1.2-6.4)**	**0.9 (0.5-1.7)**

Other Infiltrate#	**19 (61)**	**28 (41)**	**35 (34)**	**3.1 (1.3-7.2)**	**1.4 (0.7-2.6)**
Peribronchial thickening	5 (16)	5 (7)	5 (5)	3.8 (1.1-14.1)	1.6 (0.4-5.6)
Reticulo-nodular infiltrate	2 (6)	3 (4)	3 (3)	2.3 (0.4-14.6)	1.6 (0.3-7.9)
Reticular infiltrate	12 (39)	19 (28)	22 (21)	2.4 (1.0-5.5)	1.4 (0.7-2.9)
Miliary infiltrate (nodules < 2mm)	4 (13)	3 (4)	8 (8)	1.8 (0.5-6.4)	0.6 (0.1-2.2)
Large nodular infiltrate (nodules > 2mm)	1 (3)	0 (0)	0 (0)	1.0	1.0
Perihilar streakiness	2 (6)	5 (7)	5 (5)	1.4 (0.3-7.4)	1.6 (0.4-.7)
Ground glass infiltrate	1 (3)	2 (3)	3 (3)	1.1 (0.1-11.2)	1.0 (0.2-6.3)
Other infiltrate only~	**9 (29)**	**21 (31)**	**23 (22)**	**1.4 (0.6-3.6)**	**1.6 (0.8-3.1)**
Chronic Lung	**0 (0)**	**0 (0)**	**1 (1)**	**1.0**	**1.0**
Fibroses	0 (0)	0 (0)	0 (0)	-	-
Bronchiectasis	0 (0)	0 (0)	0 (0)	-	-
Cavities	0 (0)	0 (0)	1 (1)	1.0	1.0

Intrathoracic Lymphadenopathy	**5 (16)**	**13 (19)**	**17 (16)**	**0.9 (0.3-2.9)**	**1.2 (0.5-2.7)**
Hilar or mediastinal masses	2 (6)	4 (6)	8 (8)	0.8 (0.2-4.1)	0.8 (0.2-2.6)
Hilar elevation	0 (0)	0 (0)	0 (0)	-	-
Mediastinal shift	0 (0)	0 (0)	0 (0)	-	-
Tracheal or bronchial compression	2 (6)	3 (4)	2 (2)	3.5 (0.5-26.1)	2.4 (0.4-14.5)
Unilateral air-trapping	1 (3)	0 (0)	0 (0)	1.0	1.0
Lobar collapses	0 (0)	0 (0)	0 (0)	-	-
Doughnut sign	3 (10)	12 (18)	16 (15)	0.6 (0.2-2.2)	1.2 (0.5-2.7)
Bilateral air trapping	**4 (13)**	**11 (16)**	**17 (16)**	**0.8 (0.2-2.4)**	**0.9 (0.4-2.3)**
Cardiomegaly	**2 (6)**	**4 (6)**	**4 (4)**	**1.7 (0.3-9.8)**	**1.6 (0.4-6.5)**
Normal^	1 (3)	15 (22)	25 (24)	**8.5 (1.1-67.5)**	**0.9 (0.4-1.9)**

*****Airspace disease and/or pleural disease, may include other infiltrate only
Other infiltrate may or may not include CXR-PEP
~ Other infiltrate without CXR-PEP
^ Absence of airspace disease, pleural disease, other infiltrate, chronic lung disease, intrathoracic lymphadenopathy and bilateral air trapping

Table 7.4 Chest X-ray Findings in Children 12-59 months (age category 3) hospitalized for WHO-defined severe or very severe pneumonia, stratified by HIV status

Chest X-ray Pattern	**HIV-infected N= 31(%)**	**HEU N=63 (%)**	**HIV-unexposed N=118 (%)**	**HIV-infected vs HIV-unexposed OR (95% CI)**	**HEU vs HIV-unexposed OR (95% CI)**
Airspace disease	**18 (58)**	**20 (32)**	**40 (34)**	**2.7 (1.2-6.1)**	**0.9 (0.5-1.7)**
Segmental/sub segmental consolidation	7 (23)	3 (5)	8 (7)	4.0 (1.3-12.1)	0.7 (0.2-2.7)
Lobar consolidation	8 (26)	10 (16)	25 (21)	1.3 (0.5-3.2)	0.7 (0.3-1.6)
Multi-lobar consolidation	4 (13)	8 (13)	6 (5)	2.8 (0.7-10.5)	2.7 (0.9-8.2)
Volume loss/lung collapse	3 (10)	8 (13)	14 (12)	0.8 (0.2-2.9)	1.1 (0.4-2.7)
Expansion/bulging fissure	0 (0)	0 (0)	0 (0)	-	-
Lung abscess	0 (0)	0 (0)	0 (0)	-	-
Pleural Disease	**4 (13)**	**4 (6)**	**3 (3)**	**5.7 (1.2-26.9)**	**2.5 (0.6-11.9)**
Pneumothorax	1 (3)	0 (0)	0 (0)	1.0	1.0
Pleural effusion	3 (10)	4 (6)	3 (3)	4.1 (0.8-12.4)	2.6 (0.6-11.9)
Pleural plaques/calcification	0 (0)	0 (0)	0 (0)	-	-
CXR-PEP*	**18 (58)**	**20 (32)**	**40 (34)**	**2.7 (1.2-6.1)**	**0.9 (0.5-1.7)**

Other Infiltrate#	**17 (55)**	**23 (37)**	**41 (35)**	**2.3 (1.0-5.1)**	**1.1 (0.6-1.1)**
Peribronchial thickening	1 (3)	6 (10)	13 (11)	0.3 (0.0-2.1)	0.9 (0.3-2.4)
Reticulo-nodular infiltrate	2 (6)	4 (6)	5 (4)	1.6 (0.3-8.4)	1.5 (0.4-5.9)
Reticular infiltrate	9 (29)	13 (21)	23 (19)	1.7 (0.7-4.2)	1.1 (0.5-2.3)
Miliary infiltrate (nodules < 2mm)	7 (23)	6 (10)	9 (8)	3.5 (1.2-10.4)	1.3 (0.4-3.8)
Large nodular infiltrate (nodules > 2mm)	1 (3)	0 (0)	2 (2)	1.9 (0.2-22.0)	1.0
Perihilar streakiness	2 (6)	6 (10)	8 (7)	0.9 (0.2-4.7)	1.4 (0.5-4.4)
Ground glass infiltrate	1 (3)	2 (3)	1 (1)	3.9 (0.2-64.1)	3.8 (0.3-43.3)
Other infiltrate only~	**10 (32)**	**17 (27)**	**28 (24)**	**1.5 (0.7-3.6)**	**1.2 (0.6-2.4)**
Chronic Lung	**4 (13)**	**2 (3)**	**2 (2)**	**8.6 (1.5-49.3)**	**1.9 (0.3-13.8)**
Fibroses	0 (0)	0 (0)	0 (0)	-	-
Bronchiectasis	4 (13)	2 (3)	1 (1)	17.3 (1.9-161.3)	3.8 (0.3-43.2)
Cavities	0 (0)	0 (0)	1 (1)	1.0	1.0

Intrathoracic Lymphadenopathy	**9 (29)**	**11 (18)**	**32 (27)**	**1.1 (0.5-2.6)**	**0.6 (0.3-1.2)**
Hilar or mediastinal masses	2 (6)	7 (11)	17 (14)	0.4 (0.1-1.9)	0.7 (0.3-1.9)
Hilar elevation	0 (0)	0 (0)	0 (0)	-	-
Mediastinal shift	0 (0)	0 (0)	0 (0)	-	-
Tracheal or bronchial compression	1 (3)	2 (3)	3 (3)	1.3 (0.1-12.7)	1.3 (0.2-7.7)
Unilateral air-trapping	0 (0)	0 (0)	1 (1)	1.0	1.0
Lobar collapses	1 (3)	0 (0)	1 (1)	3.9 (0.2-64.2)	1.0
Doughnut sign	4 (9)	13 (9)	15 (7)	1.1 (0.4-2.6)	0.6 (0.3-1.4)
Bilateral air trapping	**3 (10)**	**10 (16)**	**19 (16)**	**0.6 (0.2-2.0)**	**1.0 (0.4-2.2)**
Cardiomegaly	**3 (10)**	**1 (2)**	**4 (3)**	**3.1 (0.6-14.4)**	**0.5 (0.1-4.2)**
Normal^	1 (3)	17 (27)	29 (25)	**11.1 (1.4-87.7)**	**1.1 (0.6-2.3)**

*****Airspace disease and/or pleural disease, may include other infiltrate only
Other infiltrate may or may not include CXR-PEP
~ Other infiltrate without CXR-PEP
^ Absence of airspace disease, pleural disease, other infiltrate, chronic lung disease, intrathoracic lymphadenopathy and bilateral air trapping

7.1.5 Chest X-ray patterns Stratified by HIV Status and Age Categories

Due to the possible differences in pneumonia etiology by immune status and HIV-exposure status, we further analysed each of the 3 HIV groups by the different age-group strata. Due to the low numbers of HIV-infected group (n=108), we limited this analyses to the main chest X-ray patterns.

In the HIV-unexposed group, children in age category 3 had a higher prevalence of lymphadenopathy (27%) compared to children in age categories 1 (9%) and 2 (16%) respectively, ($p<0.001$); but were similar for other features; Table 7.5.

Among HIV-infected children, bilateral air trapping was more common in age category 1 children (30%) compared age category 2 (13%) or age category 3 children (10%; $p=0.043$). In contrast, among HIV-infected children radiological evidence of chronic lung disease was more common among age category 3 (13%) than in age category 1 (0%) or age category 2 (2%; $p= 0.031$); Table 7.5.

7.1.6 Distribution of airspace disease and other infiltrate on chest X-ray

Air space disease was predominantly focal (confined to 1 zone): age category 1 (46%-61%), age category 2 (46%-52%) and age category 3 (45%-70%). In contrast to this, the distribution of other infiltrate was predominantly multifocal (involving 2 to 4 zones): age category 1 (53%-56%), age category 2 (57%-58%) and age category 3 (41-52%). Refer Table 7.6.

Table 7.5 Chest X-Ray Findings in Children hospitalized for WHO-defined severe or very severe pneumonia analysed by HIV Exposure Status and Age Categories

	HIV				**HEU**				**HIV-unexposed**			
Chest X-ray Pattern	**Age Cat1 N=46 (%)**	**Age Cat2 N=31 (%)**	**Age Cat3 N=31 (%)**	***P* value**	**Age Cat1 N=153 (%)**	**Age Cat2 N=68 (%)**	**Age Cat3 N=63 (%)**	***P* value**	**Age Cat1 N=206 (%)**	**Age Cat2 N=104 (%)**	**Age Cat3 N=118 (%)**	***P* value**
Airspace disease	27 (59)	20 (65)	18 (58)	0.842	46 (30)	25 (37)	20 (32)	0.615	82 (40)	41 (39)	40 (34)	0.545
Pleural disease	1 (2)	3 (10)	4 (13)	0.180	3 (2)	2 (3)	4 (6)	0.245	4 (2)	2 (2)	3 (3)	0.926
CXR-PEP	27 (59)	20 (65)	18 (58)	0.842	49 (32)	25 (37)	20 (32)	0.762	82 (40)	41 (39)	40 (34)	0.545
Other infiltrate	19 (41)	19 (61)	17 (55)	0.199	52 (34)	28 (41)	23 (37)	0.590	55 (27)	35 (34)	41 (35)	0.236
Other infiltrate only	10 (22)	9 (29)	10 (32)	0.563	39 (25)	21 (31)	17 (27)	0.707	37 (18)	23 (22)	28 (24)	0.421
Chronic lung disease	1 (2)	0 (0)	4 (13)	**0.031**	2 (1)	0 (0)	2 (3)	0.302	2 (1)	1 (1)	2 (2)	0.822
Lymphadenopathy	4 (9)	5 (16)	9 (29)	0.063	17 (11)	13 (19)	11 (17)	0.218	19 (9)	17 (16)	32 (27)	**0.000**
Bilateral air trapping	14 (30)	4 (13)	3 (10)	**0.043**	21 (14)	11 (16)	10 (16)	0.861	24 (12)	17 (16)	19 (16)	0.396
Cardiomegaly	1 (2)	2 (6)	3 (10)	0.358	10 (7)	4 (6)	1 (2)	0.325	10 (5)	4 (4)	4 (3)	0.801
Normal chest X-ray	5 (11)	1 (3)	1 (3)	0.280	49 (32)	15 (22)	17 (27)	0.303	69 (34)	25 (24)	29 (24)	0.111

Cat=category

Age categories: 1=1-5 months; 2=6-11 months; 3= 12-59 months

Table 7.6 Chest X-ray Pattern distribution of air space disease and other infiltrate in each age category, in children hospitalized for WHO-defined severe or very severe pneumonia

Chest X-ray Pattern	**Age Category 1**			**Age Category 2**			**Age Category 3**		
Air space disease	**HIV-infected N=27 (%)**	**HEU N=46 (%)**	**HIV-unexposed N=82 (%)**	**HIV-infected N=20 (%)**	**HEU N=25 (%)**	**HIV-unexposed N=41 (%)**	**HIV-infected N=18 (%)**	**HEU N=20 (%)**	**HIV-unexposed N=40 (%)**
Focal	15 (56)	21 (46)	50 (61)	10 (50)	13 (52)	19 (46)	9 (50)	9 (45)	28 (70)
Multifocal	10 (37)	24 (52)	29 (35)	8 (40)	11 (44)	20 (49)	9 (50)	11 (55)	12 (30)
Diffuse	2 (7)	1 (2)	3 (4)	2 (10)	1 (4)	2 (5)	0 (0)	0 (0)	0 (0)
Other infiltrate	**HIV-infected N=19 (%)**	**HEU N=52 (%)**	**HIV-unexposed N=55 (%)**	**HIV-infected N=19 (%)**	**HEU N=28 (%)**	**HIV-unexposed N=35 (%)**	**HIV-infected N=17 (%)**	**HEU N=23 (%)**	**HIV-unexposed N=41 (%)**
Focal	0 (0)	2 (4)	2 (3)	1 (5)	1 (4)	1 (3)	0 (0)	0 (0)	0 (0)
Multifocal	10 (53)	29 (56)	30 (55)	11 (58)	16 (57)	20 (57)	7 (41)	12 (52)	19 (46)
Diffuse	9 (47)	21 (40)	23 (42)	7 (37)	11 (39)	14 (40)	10 (59)	11 (48)	22 (54)

Disease focal if confined to 1 zone, multi-focal 2-4 zones and diffuse >4 zones

7.2 Discussion: Objective 2

The most common chest X-ray finding in all children hospitalized with WHO-defined severe or very severe pneumonia in the era of HiB and PCV immunization was CXR-PEP. This was predominantly due to air space disease, the more common finding being lobar consolidation, and was consistent across all 3 HIV-exposure groups and between the different age categories. Furthermore, CXR-PEP was twice as common in HIV-infected compared with HIV-unexposed children. These data suggest that bacterial pneumonia, using CXR-PEP as a proxy measure thereof, remains a major contributor of hospitalization for childhood pneumonia in settings such as ours where PCV immunization is included in the public immunization program.

The epidemiological settings of childhood pneumonia described in the literature review differ by way of prevalence of HIV-infection, median age of children included, percentage inclusion of ambulatory and hospitalized children, use of HiBCV and PCV in the public immunization programs, prevalence of malnutrition, disease severity, timing of hospitalization, prior antibiotic usage and lack of standardized chest X-ray reporting (60-62, 104, 122, 153). All of these factors are potential confounders that need to be considered when comparing results on chest X-ray findings between the different studies.

Our findings of CXR-PEP being the most common finding in all children hospitalized with WHO-defined severe or very severe pneumonia, regardless of HIV-exposure status is comparable to the literature pre-PCV introduction where air space consolidation ranged from 40-75% (59-62). Our results are also comparable to the only study to describe chest X-ray findings in HEU children hospitalized with pneumonia by Jeena *et al* from South Africa during the pre-

PCV immunization era, in which chest X-ray interpretation was also based on WHO standardized chest X-ray interpretation criteria (15, 67). Similar to our study, CXR-PEP was evident among 35% HIV-unexposed, 40% HEU and 55% HIV-infected children. Also, similar to our study, CXR-PEP was 2.3 fold (95% CI 1.3-4.0) more common in HIV-infected children compared to HIV-unexposed children, and there was no difference between HEU and HIV-unexposed children although there were limited number of HEU children (n=40) enrolled (67). Our study findings is further supported by another recent study by Kelly *et al* in Botswana post PCV introduction, who too documented that HIV-infected children were more likely to have CXR-PEP (64%) compared to HIV-uninfected children (32%; p=0.004), although the study did not evaluate specifically for HEU children (66).

Despite South Africa having introduced PCV into its public immunization program, our findings in HIV-infected children are similar to that described by Madhi *et al* from the same study population between 1997 and 1998 prior to PCV immunization or ART treatment of HIV-infected children. Similar to this study, they too reported that air space/alveolar consolidation was the most common finding, and was twice as common in HIV-infected children (64%) compared to HIV-uninfected children (42%) (62); comparable to the findings in our study where CXR-PEP was prevalent in 38% of HIV-unexposed and 60% HIV-infected children. This, despite PCV having demonstrated vaccine efficacy against of chest X-ray confirmed pneumonia of 20% in HIV-uninfected and 13% in HIV-infected South African children (16).

Possible reasons for our current study findings could be that although the number of hospitalizations for all cause pneumonia may have decreased in the study population post PCV introduction (154), bacteria are still responsible for a sizable percentage of the residual

pneumonia cases requiring hospitalisation; hence the predominant chest X-ray pattern has not changed. Furthermore, respiratory viruses, opportunistic infections and poly-microbial infections may also cause air space consolidation on chest X-ray. This is supported by studies which demonstrated no significant association between chest X-ray pattern and putative microbiological etiology, (63, 64, 68, 94), albeit the caveat of the absence of a sensitive "gold standard" test with which to make the microbiological diagnosis for bacterial pneumonia etiology.

Our study finding of CXR-PEP being twice as common in HIV-infected compared to HIV-uninfected children is consistent with other studies (62, 66, 67). Compared to HIV-uninfected children, HIV-infected children have higher risk of childhood CAP caused by *Streptococcus pneumoniae*, Gram-negative bacteria, PTB and increased opportunistic disease such as *Pneumocystis jiroveci* pneumonia, which may manifest as CXR-PEP (32, 66, 155-157). This is further supported by a recent review article by Pitcher *et al* on the chest X-ray features of chronic respiratory disease in HIV-infected children in which homogenous air space opacification was the commonest chest X-ray feature (45%) between 7 studies of children diagnosed with *Pneumocystis jiroveci* pneumonia (109).

Madhi *et al* also found that reticular-nodular infiltrate was 10-fold more common in HIV-infected children compared to HIV-uninfected children (62). This too was consistent with the results of our study, where in addition to other infiltrate being more common in HIV-infected children compared to HIV-unexposed children, reticular pattern and miliary infiltrate was twice as common in HIV-infected compared with HIV-unexposed children. This is, however, in contrast to the findings of Jeena *et al* who found other infiltrate being less prevalent in HIV-infected (45%; OR 0.4; 95% CI 0.3-0.8) than HIV-unexposed children (65%) (67).

Chronic lung disease was uncommon in all 3 HIV groups, but 4 times more common in HIV-infected children compared with HIV-unexposed children. Furthermore chronic lung disease was 8 times more common in HIV-infected children compared to HIV-unexposed children in the age group 12 to 59 months. This supports the findings by Pitcher *et a*l that HIV-infected children have an increased risk of developing chronic lung disease due to risk factors such as increased incidence and severity of acute chest infections, aspiration pneumonia, increased risk for PTB, cardiovascular disease and lymphocytic interstitial pneumonitis (109). The low prevalence of chronic lung disease reported in our study could be explained due to the younger population group (mean age of 9.0 months). This is supported by chronic lung disease being more common among older HIV-infected children compared to younger HIV-infected children in our study. Nortan *et a*l investigating 86 HIV-infected children in the USA using serial chest X-rays found a cumulative incidence of 33% of chronic lung changes on chest X-ray at 48 months of age, with a median age of onset of 18 months (117).

Intrathoracic lymphadenopathy was prevalent in 14-17% of children with no significant difference between HIV-infected compared to HIV-unexposed children, or between HEU and HIV-unexposed children. Our results on the prevalence of hilar lymphadenopathy are similar to the literature in countries with a high TB prevalence (61, 62, 66).

Madhi *et al* reported a higher prevalence of bilateral air trapping (41%-42%) (62), compared to our study (14%-19%). A possible reason for this difference was the exclusion in our study of children hospitalized with severe pneumonia and wheeze who responded to bronchodilator therapy, which could have selected out children with bilateral air trapping from our study. A limitation of the study by Madhi *et al* used was the use of one chest X-ray reader creating observational bias (62).

The presence of pleural effusion was uncommon (2-7%) in our study and lower than reported by others (16-32%) (59, 60, 66). This could be due to the younger median age in our study population or variability in chest X-ray interpretation criteria used in the different studies. In our study we defined pleural effusion using the WHO standardized chest X-ray interpretation criteria (15), as fluid in the pleural space which may be at the costo-phrenic angle or as a layer adjacent to the lateral chest wall, but not in the horizontal or oblique fissures (15).

Even in the era of antiretroviral therapy with South Africa having one of the largest national anti-retroviral therapy program in the world, within the HIV-infected group only 29% were on anti-retroviral therapy prior to hospitalization, the majority (82%) of whom were severely immune suppressed. Hence we could not compare chest X-ray findings of HIV-infected children between the WHO immune categorization groups.

Madhi *et al* found that HIV-uninfected children were more likely to have a normal chest X-ray (18%) compared to HIV-infected children (7%) (62), which too was consistent with our study 29% vs 6%, respectively) and which was evident across all 3 age groups. Further literature findings by Pitcher *et al* investigating HIV-infected children with advanced clinical disease and immune suppression where 77% were not on ART; who had no clinical features of acute respiratory illness found that 84% had abnormal chest X-rays, 51% grade 2 changes including pulmonary opacification (28%), reticulo-nodular infiltrate and opacification (12%) and 33% had grade 1 changes ie: bronchial thickening (14). Similarly Nortan *et a*l investigating HIV-infected children found a cumulative incidence of 33% of chronic lung changes on chest X-ray; with a median age of onset of 18 months (117), although these 2 studies performed in ambulant HIV-infected children cannot be directly extrapolated to our study findings performed in acutely ill hospitalized HIV-infected children with WHO defined severe or very severe pneumonia.

7.3 Limitations: Objective 2

Limitations of our study include that a frontal and lateral chest X-ray combination was only available in 58% of children. Lateral chest X-rays are performed in children investigated for pneumonia as they may improve the detection of lymphadenopathy (142). Hence the prevalence of lymphadenopathy in children who had a frontal chest X-ray only may have been underestimated. Furthermore, since the readers were blinded to all clinical information including age, for cardiomegaly we used criteria of a cardiothoracic ratio of ≥50%, which might have over-estimated the prevalence of cardiomegaly. Nevertheless, we identified a low prevalence of cardiomegaly (4%-6%).

A further limitation of our study was that comparisons between the HIV-exposure groups and age need to be interpreted with caution due to the limited number of HIV-infected children (n=108) enrolled. Hence we had limited power to evaluate for chest X-ray pattern differences between the 3 age categories in HIV-infected children.

7.4 Future Research: Objective 2

Future research would involve re-evaluating the set of South African PERCH chest X-rays using the proposed clarifications to the original WHO chest x-ray definitions, proposed by the current WHO Chest Radiography in Epidemiological Studies (CRES) project. These proposed clarifications relate to the size of the opacity and the inclusion of the silhouette sign in the endpoint consolidation definitions. The CRES project is currently a work in progress.

8 Objective 3: Chest X-ray Patterns by Clinical Parameters: Results, Discussion, Limitations

Objective: To determine the association of chest X-ray patterns with clinical symptoms and signs, HIV exposure status, acute phase reactants and clinical outcomes in children hospitalized with WHO-defined severe or very severe community acquired pneumonia

8.1 Clinical Results

As described in the methods, chapter 5, descriptive statistics, e.g. median age in months with interquartile ranges, and comparison of medians were performed using the Wilcoxon rank sum test for non-parametric data. For this analysis a Bonferroni correction was done, with adjusted *p*-values <0.025 taken as statistically significant. HIV-infected and HEU children were compared with HIV-unexposed children as the reference group where applicable.

The demographic data of the children in each of the age categories stratified by HIV status are detailed in Tables 8.1 to 8.3. Among children in **age category 1** compared to HIV-unexposed, HIV-infected children were older (median age: 3 months vs 2 months; $p= 0.024$), had a higher prevalence of severe malnutrition (41% vs 21%; $p=0.003$), hypoxia (94% vs 79%; $p=0.025$) and death within 30 days of hospitalization (21% vs 4%; $p<0.001$), but a lower prevalence of wheezing (15% vs 31%; $p=0.029$). HEU children in the age category 1 were similar to HIV-unexposed cases, except for higher prevalence of severe malnutrition (35% vs 21%; $p=0.003$) and a lower prevalence of crackles (56% vs 73%; $p<0.001$) and wheezing (20% vs 31%; $p=0.017$). Refer Table 8.1.

Compared with HIV-unexposed children in **age category 2**, HIV-infected children had a higher prevalence of severe malnutrition (63% vs 28%; $p<0.001$), and death within 30 days of hospitalization (35% vs 2%; $p<0.001$), but a lower prevalence of tachypnea (55% vs 84%; $p= 0.001$) and wheezing (13% vs 40%; $p= 0.007$). HEU in the age category 2 were similar to HIV-unexposed children. Refer Table 8.2.

In **age category 3**, the groups were largely similar for demographic features, but compared to HIV-unexposed children, HIV-infected children had a higher prevalence of severe malnutrition (55% vs 19%; $p<0.001$), and a lower prevalence of being fully vaccinated for PCV (60% vs 85%; $p=0.003$) and wheezing (20% vs 50%; $p= 0.004$); refer Table 8.3.

Table 8.1 Demographic, clinical and laboratory features of infants 1-5 months of age hospitalized for severe or very severe pneumonia, stratified by HIV Status.

Clinical Parameters	**HIV-infected N=46 (%)**	**HEU^ N=153 (%)**	**HIV-unexposed N=206 (%)**	**HIV-infected vs HIV-unexposed *P* Value**	**HEU^ vs HIV-unexposed *P* Value**
Median age months	3 (IQR* 2-4)	2 (IQR*1-4)	2 (IQR*1-3)	**0.024**	0.512
Female	27 (59)	73 (48)	103 (50)	0.286	0.668
PCV immunization status					
no vaccine	9 (20)	60 (41)	75 (37)	0.075[#]	0.616[#]
partially vaccinated	28 (62)	67 (46)	93 (46)		
fully vaccinated	8 (18)	19 (13)	33 (16)		
Hib[&] immunization status					
no vaccine	14 (31)	56 (38)	85 (42)	0.301[x]	0.323[x]
partially vaccinated	26 (58)	77 (53)	91 (45)		
fully vaccinated	5 (11)	13 (9)	25 (12)		
Severe Malnutrition[a]	19 (41)	53 (35)	42 (21)	**0.003**	**0.003**
Fever[b]	30 (65)	90 (59)	110 (53)	0.145	0.306
Hypoxia[c]	43 (94)	114 (75)	162 (79)	**0.025**	0.274
Tachypnea[d]	35 (80)	106 (72)	146 (74)	0.422	0.736
Crackles	24 (52)	84 (56)	148 (73)	0.064	**0.001**
Wheezing	7 (15)	30 (20)	63 (31)	**0.029**	**0.017**
CRP≥40 mg/dL	12 (27)	24 (16)	39 (19)	0.256	0.432
Leucocytosis[e]	25 (54)	65 (42)	77 (37)	0.034	0.328
Antibiotic serum activity[f]	24 (56)	73 (50)	96 (48)	0.368	0.700
Hospital stay ≥3 days	45 (98)	148 (97)	194 (94)	0.311	0.259
Mechanical ventilation	6 (13)	18 (12)	17 (8)	0.308	0.267
Death within 30 days of hospitalization	9 (21)	6 (5)	7 (4)	**<0.001**	0.792

^HEU: HIV-exposed, uninfected

*IQR- interquartile range

[&]*Haemophilus influenzae* type b;

[#]PCV unvaccinated and partially vaccinated compared to PCV fully vaccinated as reference;

[x]Hib unvaccinated and partially vaccinated compared to Hib fully vaccinated as reference;

[a]Severe Malnutrition: Weight-for-age Z-score ≤-3 standard deviations (SD) below the mean using WHO growth standards;

[b]Fever: axillary temperature >38 ºC on admission, or history of fever in the past 48 hours;

[c]Hypoxia: O_2 saturations <90% on room air on admission, or supplemental O_2 requirement;
[d]Tachypnea: Age <2 months respiratory rate (RR) >60 breaths per minute; Age 2-11 months RR >50 breaths per minute;
[e]Leucocytosis: For age categories 1 and 2: white cell count $>15 \times 10^9$/L;
[f]Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter >6mm

Table 8.2 Demographic, clinical and laboratory features of children 6-11 months of age hospitalized for severe or very severe pneumonia, stratified by HIV Status.

Clinical Parameters	**HIV-infected N=31 (%)**	**HEU^ N=68 (%)**	**HIV-unexposed N=104 (%)**	**HIV-infected vs HIV-unexposed *P* Value**	**HEU^ vs HIV-unexposed *P* Value**
Median age months	8 (IQR* 7-10)	8 (IQR* 6-9)	7.5 (IQR* 7-9.5)	0.354	0.431
Female	15 (48)	33 (49)	41 (39)	0.374	0.238
PCV immunization status					
no vaccine	1 (3)	2 (3)	3 (3)		
partially vaccinated	6 (21)	11 (19)	27 (28)	0.760[#]	0.482[#]
fully vaccinated	22 (76)	45 (78)	68 (69)		
Hib[&] immunization status					
no vaccine	1 (3)	2 (3)	6 (6)	0.768 [x]	0.713 [x]
partially vaccinated	9 (31)	19 (33)	34 (35)		
fully vaccinated	19 (66)	37 (64)	58 (59)		
Severe Malnutrition[a]	19 (63)	21 (31)	29 (28)	**<0.001**	0.672
Fever[b]	28 (90)	42 (62)	78 (75)	0.068	0.065
Hypoxia[c]	20 (65)	52 (76)	82 (79)	0.103	0.713
Tachypnea[d]	17 (55)	47 (69)	86 (84)	**0.001**	0.027
Crackles	25 (81)	41 (61)	73 (72)	0.351	0.132
Wheezing	4 (13)	29 (43)	40 (40)	**0.007**	0.635
CRP≥40 mg/dL	13 (42)	19 (28)	33 (32)	0.326	0.541
Leucocytosis[e]	17 (57)	27 (40)	51 (49)	0.462	0.229
Antibiotic serum activity[f]	21 (68)	27 (43)	50 (51)	0.093	0.342
Hospital stay ≥3 days	27 (87)	62 (91)	96 (92)	0.371	0.791
Mechanical ventilation	1 (3)	7 (10)	8 (8)	0.382	0.554
Death within 30 days of hospitalization	8 (35)	3 (5)	2 (2)	**<0.001**	0.292

^HEU: HIV-exposed, uninfected

*IQR- interquartile range

[&]*Haemophilus influenzae* type b;

[#]PCV unvaccinated and partially vaccinated compared to PCV fully vaccinated as reference;

[x]Hib unvaccinated and partially vaccinated compared to Hib fully vaccinated as reference;

[a]Severe Malnutrition: Weight-for-age Z-score ≤-3 standard deviations (SD) below the mean using WHO growth standards;

[b]Fever: axillary temperature >38 ºC on admission, or history of fever in the past 48 hours;

[c]Hypoxia: O_2 saturations <90% on room air on admission, or supplemental O_2 requirement;
[d]Tachypnea: Age 2-11 months RR >50 breaths per minute;
[e]Leucocytosis: For age categories 1 and 2: white cell count $>15 \times 10^9$/L;
[f]Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter >6mm

Table 8.3 Demographic, clinical and laboratory features of Children 12-59 months of age hospitalized for severe or very severe pneumonia, stratified by HIV Status.

Clinical Parameters	**HIV-infected N=31 (%)**	**HEU^ N=63 (%)**	**HIV-unexposed N=118 (%)**	**HIV-infected vs HIV-unexposed *P* Value**	**HEU^ vs HIV-unexposed *P* Value**
Median age months	22 (IQR*16-38)	18 (IQR*14-26)	19 (IQR*15-26)	0.113	0.440
Female	11 (35)	29 (46)	56 (47)	0.233	0.855
PCV no vaccine	9 (36)	6 (11)	10 (9)	**0.003**[#]	0.738[#]
partially vaccinated	1 (4)	4 (7)	5 (5)		
fully vaccinated	15 (60)	45 (82)	92 (86)		
Hib[&] no vaccine	4 (15)	5 (9)	8 (7)	0.053 [x]	0.720 [x]
partially vaccinated	1 (4)	0 (0)	0 (0)		
fully vaccinated	21 (81)	50 (91)	99 (93)		
Severe Malnutrition[a]	17 (55)	18 (29)	22 (19)	**<0.001**	0.111
Fever[b]	24 (77)	42 (67)	77 (65)	0.197	0.849
Hypoxia[c]	22 (71)	39 (62)	83 (72)	0.949	0.186
Tachypnea[d]	28 (90)	57 (90)	106 (91)	0.963	0.979
Crackles	22 (73)	39 (64)	73 (63)	0.312	0.952
Wheezing	6 (20)	21 (34)	57 (50)	**0.004**	0.054
CRP≥40 mg/dL	14 (45)	26 (42)	36 (31)	0.149	0.157
Leucocytosis[e]	17 (57)	35 (56)	57 (49)	0.462	0.412
Antibiotic serum activity[f]	13 (45)	30 (53)	57 (50)	0.648	0.705
Hospital stay ≥3 days	29 (94)	54 (86)	98 (83)	0.143	0.642
Mechanical ventilation	0 (0)	5 (8)	5 (4)	0.244	0.299
Death within 30 days of hospitalization	3 (10)	1 (2)	3 (3)	0.082	0.696

^HEU: HIV-exposed, uninfected
*IQR- interquartile range
[&]*Haemophilus influenzae* type b;
[#]PCV unvaccinated and partially vaccinated compared to PCV fully vaccinated as reference;
[x]Hib unvaccinated and partially vaccinated compared to Hib fully vaccinated as reference;
[a]Severe Malnutrition: Weight-for-age Z-score ≤-3 standard deviations (SD) below the mean using WHO growth standards;
[b]Fever: axillary temperature >38 ºC on admission, or history of fever in the past 48 hours;

[c]Hypoxia: O_2 saturations <90% on room air on admission, or supplemental O_2 requirement;
[d]Tachypnea: Age >12 months RR >40 breaths per minute;
[e]Leucocytosis: For age category 3: white cell count $>13 \times 10^9$/L;
[f]Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter >6mm

8.1.1 Results: The association of chest X-ray patterns with clinical symptoms and signs, HIV exposure status, acute phase reactants and clinical outcomes

As detailed in the methods, comparisons with two-sided *p*-values <0.2 in univariate analyses were incorporated into multivariate analyses, using stepwise logistic regression to determine the independent effects of variables. This led to adjusting for age, HIV exposure status, nutritional status, hypoxia (low oxygen saturation), age-adjusted presence of tachypnea and presence of wheezing in the multiple logistic regression models.

8.1.2 Chest X-Ray Primary End Point Pneumonia (CXR-PEP) vs no Chest X-Ray Primary End Point Pneumonia (CXR-PEP)

Cases with CXR-PEP compared to cases with absence of CXR-PEP, were more likely to be severely malnourished (39% vs 24%, aOR 1.9; 95% CI 1.4-2.7) and to be febrile (71% vs 60%, aOR 1.8; 95% CI 1.3-2.4). Furthermore, children with CXR-PEP were 2-fold more likely to be HIV-infected (aOR 2.3, 95% CI 1.5-3.6), but 40% less likely (29% vs 38%, aOR 0.6; 95% CI 0.5-0.9), to be HEU; Table 8.4. Conversely, children with CXR-PEP compared to cases without CXR-PEP were less likely to be fully vaccinated with PCV (40% vs 48%, aOR 0.7; 95% CI 0.5-1.0) and were less likely to present with wheezing (21% vs 39%, aOR 0.5; 95% CI 0.3-0.7). The presence of CXR-PEP was not associated with hypoxia (76% vs 76%), tachypnea (78% vs 78%) and crackles on chest all auscultation (68% vs 65%) among the CXR-PEP compared to non CXR-PEP cases; refer Table 8.4.

Cases with CXR-PEP were more likely to have CRP $\geq$ 40mg/dL (40% vs 19%, aOR 3.2; 95% CI 2.2-4.5), and positive serum antimicrobial activity (55% vs. 47%, aOR 1.3; 95% CI 1.0-1.9) compared to non CXR-PEP cases. Cases with CXR-PEP also trended towards leucocytosis (49% vs 43%, aOR 1.2; 95% CI: 0.9-1.6).

Cases with CXR-PEP were more 2.8 fold more likely to require mechanical ventilation (14% vs 5%, aOR 2.8; 95% CI 1.6-4.8). Furthermore, although not significant, cases with CXR-PEP also trended to have higher case fatality ratio within 30 days of hospitalization (9% vs 4%, aOR 1.4; 95% CI 0.7-0.3) and hospital stay duration of ≥ 3 days (94% vs 91%, aOR 1.5; 95% CI 0.9-2.7); refer Table 8.4. Overall, cases with CXR-PEP were 2.5 fold (95% CI 1.5-4.0) more likely to have required mechanical ventilation or to have demised within 30 days of admission (composite measure); (22% vs 8%) compared to non CXR-PEP cases.

8.1.3 Other Infiltrate Only vs no other Infiltrate only

On comparison of cases in whom there was only other infiltrate compared to cases in which the chest X-ray showed no evidence of other infiltrate, cases with other infiltrate only were more likely to be fully vaccinated for PCV (56% vs 42%, aOR 1.8; 95% CI 1.2-2.8), and less likely to be partially vaccinated for PCV (24% vs 35%, aOR 0.6; 95% CI 0.4-0.9). There was a higher prevalence of HIV-unexposure in children with other infiltrate only compared to the absence thereof (45% vs 54%, aOR 0.7; 95% CI 0.5-1.0), and conversely cases with other infiltrate were more likely to be HEU (40% vs 33%, aOR 1.3; 95% CI 0.9-1.9) or HIV-infected (15% vs 13%, aOR 1.3; 95% CI 0.8-2.1), albeit this difference was not significant, refer Table 8.4.

The presence of other infiltrate only compared to no other infiltrate was not associated with any difference in prevalence of severe malnutrition (29% vs 30%), hypoxia (77% vs 75%), tachypnea (79% vs 77%), crackles (66% vs 66%) or wheezing (33% vs 32%) between the cases; refer Table 8.4.

Children with other infiltrate only were, however, 40% less likely to have CRP ≥40 mg/dL, (20% vs 29%, OR 0.6; 95% CI 0.4-0.8) compared to those without other infiltrate only. There were however, no difference observed between cases with other infiltrate only and poor clinical

outcomes including hospital stay duration ≥ 3 days (93% vs 91%; *p*=0.523), need for mechanical ventilation (7% vs 9%; *p*=0.389), or case fatality ratio within 30 days of hospitalization (9% vs 5%; *p*=0.112), or the composite measure of either requiring mechanical ventilation or death (13% vs 14%; *p*=0.961); refer Table 8.4.

8.1.4 Intrathoracic Lymphadenopathy vs no intrathoracic lymphadenopathy

The presence of intrathoracic lymphadenopathy was directly associated with age group, with there being a lower prevalence of intrathoracic lymphadenopathy in the 1- 5 month age group (32% vs 53%, aOR0.4; 95% CI 0.3-0.6), whilst being higher in the 12- 59 month age group (40% vs 23%, aOR 2.2; 95% CI 1.4-3.3). The presence of intrathoracic lymphadenopathy was also more common in children that were fully vaccinated for PCV (64% vs 42%, aOR 1.7; 95% CI 1.1-2.90); refer Table 6.2. Children with intrathoracic lymphadenopathy did not differ in prevalence of severe malnutrition (31% vs 30%), hypoxia (73% vs 76%), tachypnea (81% vs 77%), crackles (69% vs 66%) or wheezing (40% vs 31%).

Children with intrathoracic lymphadenopathy compared to those without intrathoracic lymphadenopathy did not differ in prevalence of acute phase reactants CRP ≥40mg/dL (24% vs 27%) or leucocytosis (45% vs 46%) or positive antibiotic serum activity (50% vs 50%); refer Table 6.2. The presence of intrathoracic lymphadenopathy compared to absence thereof, were less likely to be associated with need for mechanical ventilation (1% vs 9%, aOR 0.2; 95% CI 0.0-0.8) or the composite of either requiring mechanical ventilation or death (4% vs 15%, aOR 0.2; 95% CI 0.1-0.7); refer Table 8.5.

8.1.5 Bilateral air trapping vs no bilateral air trapping

Children with bilateral air trapping compared to those without bilateral air trapping were 2.3 fold more likely to have wheezing (45% vs 30%; aOR 2.3; 95% CI 1.5-3.5). The presence of bilateral

wheezing was, however, not associated with prevalence of severe malnutrition (31% vs 30%), fever (66% vs 64%), hypoxia (76% vs 76%), tachypnea (84% vs 77%) or crackles (61% vs 67%); but these cases were less likely to have a CRP ≥40 mg/dL; (18% vs 29%, aOR 0.5; 95% CI 0.3-0.9); refer Table 8.5.

The presence of bilateral air trapping observed on chest X-ray compared to absence thereof was not associated with any difference in poor prognostic outcomes including hospital stay ≥ 3 days (90% vs 92%), need for mechanical ventilation (5% vs 9%) or death within 30 days of hospitalization (4% vs 6%); refer Table 8.5.

8.1.6 Chronic Lung Disease vs no chronic lung disease

The presence of chronic lung disease was directly associated with age group, with there being a higher prevalence in the 12- 59 month age group (57% vs 25%, aOR 5.2; 95% CI 1.7-16.9).

Children with chronic lung disease were four-fold more likely to be severely malnourished (64% vs 29%, aOR 3.9; 95% CI 1.2-12.6), whilst there were no significant differences in presence of fever (64% vs 64%), hypoxia (79% vs 76%), tachypnea (71% vs 78%), crackles on auscultation (69% vs 66%) and wheezing (31% vs 32%); Table 8.6.

Children with chronic lung disease were twice as likely to have CRP ≥40mg/dL (47% vs 26%, aOR 2.1; 95% CI 1.1-4.1), although there was no difference in prevalence of leucocytosis compared to cases without chronic lung disease, Table 6.3. Furthermore, there was no difference in poor prognostic outcomes of hospital stay ≥ 3 days duration (100% vs 92%), need for mechanical ventilation (7% vs 8%), or death within 30 days of hospitalization (7% vs 6%) between cases with and without chronic lung disease; refer Table 8.6.

8.1.7 Normal chest X-ray vs any chest X-ray changes

Overall, 26% (219/858) of cases with severe or very severe clinical pneumonia were evaluated to have a normal chest X-ray, i.e. no discernible changes on chest X-ray. The presence of a normal chest X-ray was more common among the youngest age group of 1- 5 month of age (57% vs 47%, aOR 1.6; 95% CI 1.1-2.2), refer Table 8.6.

Children with the normal chest X-rays were less likely to present with severe malnutrition (21% vs 33%, aOR 0.6; 95% CI 0.4-0.9), fever (49% vs 69%, aOR 0.5; 95% CI 0.3-0.6) and tachypnea (72% vs 80%, aOR 0.6; 95% CI 0.4-0.9). However, no significant differences for presence of hypoxia (76% vs 75%) and crackles on auscultation were found (64% vs 67%); refer Table 8.6.

Cases with a normal chest X-ray compared to those with any chest X-ray changes were more likely to be HIV-unexposed children (59% vs 50%; aOR 1.3; 95% CI 1.0-1.8), and conversely HIV-infected cases were less likely to present with a normal chest X-ray (3% vs 17%; aOR 0.2; 95% CI 0.1-0.4). Cases with a normal chest X-ray compared to those with any chest X-ray changes were less likely to have CRP $\geq$40mg/dL (18% vs 30%; aOR 0.6; 95% CI 0.4-0.9) or positive antibiotic serum activity (42% vs 53%; aOR 0.6; 95% CI: 0.5-0.9). Children with normal chest X-rays were also less likely to require mechanical ventilation (4% vs 10%; aOR 0.4; 95% CI 0.2-0.8), and trended to have a lower likelihood of death (aOR 0.5; 95% CI 0.2-1.6); Table 8.6.

Table 8.4 Chest X-ray primary end-point pneumonia (CXR-PEP) and Other infiltrate only association with clinical parameters, HIV exposure status, acute phase reactants and poor prognostic outcomes in children hospitalized with WHO-defined severe or very severe pneumonia

All Children	**CXR-PEP** N=333 (%)	No CXR-PEP N=525 (%)	OR (95% CI)	Adj OR* (95% CI)	**Other infiltrate only** N=208 (%)	No Other Infiltrate Only N=650 (%)	OR (95% CI)	Adj OR* (95% CI)
Female	182 (55)	222 (42)	*p*=0.000[~]	N/A	92 (44)	312 (48)	*p*=0.343[~]	N/A
Male	151 (45)	303 (57)	*p*=0.000[~]	N/A	116 (56)	338 (52)	*p*=0.343[~]	N/A
Mean Age in months	8.75	9.22	N/A	N/A	9.48	8.90	N/A	N/A
Median Age in months (IQR[+])	5 (2-11)	6 (2-13)	*p*=0.634[#]	N/A	6 (3-13)	5 (2-11)	*p*=0.112[#]	N/A
Age 1-5 months	167 (50)	259 (49)	1.0 (0.8-1.4)	1.0 (0.7-1.3)	92 (44)	334 (51)	0.8 (0.5-1.1)	0.8 (0.6-1.1)
Age 6-11 months	87 (26)	125 (24)	1.1 (0.8-1.6)	1.2 (0.8-1.6)	58 (28)	154 (24)	1.2 (0.9-1.8)	1.2 (0.8-1.8)
Age 12-59 months	79 (24)	141 (27)	0.8 (0.6-1.2)	0.9 (0.6-1.3)	58 (28)	162 (25)	1.2 (0.8-1.7)	1.2 (0.8-1.7)
PCV unvaccinated	72/307 (23)	111/493 (23)	1.1 (0.8-1.5)	1.0 (0.7-1.5)	41/198 (21)	142/602 (24)	0.8 (0.6-1.3)	0.9 (0.6-1.4)
PCV partially vaccinated [a]	112/307 (36)	144/493 (29)	1.4 (1.0-1.9)	**1.4 (1.0-2.0)**	47/198 (24)	209/602 (35)	0.6 (0.4-0.8)	**0.6 (0.4-0.9)**
PCV fully vaccinated [b]	123/307 (40)	238/493 (48)	0.7 (0.5-1.0)	**0.7 (0.5-1.0)**	110/198 (56)	251/602 (42)	1.7 (1.3-2.4)	**1.8 (1.2-2.8)**
Severe Malnutrition [c]	129/329 (39)	126/523 (24)	2.0 (1.5-2.8)	**1.9 (1.4-2.7)**	59/206 (29)	196/646 (30)	0.9 (0.7-1.3)	0.8 (0.6-1.2)
Fever [d]	236 (71)	313 (60)	1.6 (1.2-2.2)	**1.8 (1.3-2.4)**	141 (68)	408 (63)	1.2 (0.9-1.7)	1.1 (0.8-1.6)
Hypoxia [e]	251/332 (76)	395/522 (76)	1.0 (0.7-1.4)	1.2 (0.8-1.7)	160 (77)	486/646 (75)	1.1 (0.8-1.6)	1.1 (0.7-1.6)
Tachypnea [f]	252/325 (78)	402/515 (78)	0.9 (0.7-1.4)	1.0 (0.7-1.4)	161/205 (79)	493/635 (77)	1.1 (0.7-1.5)	1.1 (0.7-1.7)
Crackles	222/325 (68)	335/517 (65)	1.2 (0.9-1.6)	1.1 (0.8-1.6)	135/204 (66)	422/638 (66)	1.0 (0.7-1.4)	1.0 (0.7-1.4)
Wheezing	69/324 (21)	201/515 (39)	0.4 (0.3-0.6)	**0.5 (0.3-0.7)**	67/202 (33)	203/637 (32)	1.1 (0.8-1.5)	1.1 (0.7-1.6)

HIV-unexposed	163/322 (51)	265/498 (53)	0.9 (0.7-1.2)	1.0 (0.7-1.3)	88/194 (45)	340/626 (54)	0.7 (0.5-1.0)	**0.7 (0.5-1.0)**
HIV-exposed uninfected (HEU)	94/322 (29)	190/498 (38)	0.7 (0.5-0.9)	**0.6 (0.5-0.9)**	77/194 (40)	207/626 (33)	1.3 (0.9-1.9)	1.3 (0.9-1.9)
HIV-infected	65/322 (20)	43/498 (9)	2.7 (1.7-4.2)	**2.3 (1.5-3.6)**	29/194 (15)	79/626 (13)	1.2 (0.8-1.9)	1.3 (0.8-2.1)
Raised CRP ≥40 mg/dL	130/327 (40)	97/518 (19)	2.9 (2.1-3.9)	**3.2 (2.2-4.5)**	42/206 (20)	185/639 (29)	0.6 (0.4-0.9)	**0.6 (0.4-0.8)**
Leucocytosis [g]	164/332 (49)	227/522 (43)	1.4 (1.1-1.9)	1.2 (0.9-1.6)	87/206 (42)	304/648 (47)	0.8 (0.6-1.1)	0.8 (0.5-1.1)
Positive Antibiotic serum activity [h]	172/314 (55)	236/504 (47)	1.4 (1.0-1.8)	**1.3 (1.0-1.9)**	106/198 (54)	302/620 (49)	1.2 (0.9-1.7)	1.2 (0.9-1.7)
Hospital stay ≥3 days	312 (94)	475 (91)	1.6 (0.9-2.7)	1.5 (0.9-2.7)	193 (93)	594 (91)	1.2 (0.7-2.2)	1.3 (0.7-2.4)
Mechanical Ventilation	46 (14)	24 (5)	3.3 (2.0-5.6)	**2.8 (1.6-4.8)**	14 (7)	56 (9)	0.8 (0.4-1.4)	0.9 (0.5-1.8)
Death within 30 days hospitalization	24/279^ (9)	20/452^ (4)	2.0 (1.1-3.8)	1.4 (0.7-3.0)	15/176^ (9)	29/555^ (5)	1.7 (0.9-3.2)	1.5 (0.7-3.3)
Mechanical ventilation or death[i]	63/289^ (22)	38/454^ (8)	3.1 (2.0-4.7)	**2.5 (1.5-4.0)**	24/178^ (13)	77/565^ (14)	1.0 (0.6-1.6)	1.1 (0.6-1.8)

*Adjusted odds ratio using a multiple logistic regression model: adjusting for age, HIV exposure status, severe malnutrition, hypoxia, tachypnea and wheeze;
[+] IQR Interquartile range;
N/A not applicable;
[~] *p* value calculated using Pearson's chi-squared test;
[#] *p* value calculated using Wilcoxon rank sum test for non-parametric data;
[^] some children were lost to follow up within the 30 day period of initial hospitalization;
[a]PCV partially vaccinated: Vaccination status based on the number of doses a child received and their age at first dose or age at vaccine introduction;
[b]PCV fully vaccinated: defined as 3 or more doses, or 2 or more doses for a child aged 12 to 24 months at either first dose of vaccine or at vaccine introduction, or 1 or more doses for a child aged 24 months or older at either first dose of vaccine or at vaccine introduction;
[c]Severe Malnutrition: Weight-for-age less than -3 z-scores below the median of the WHO child growth standards;
[d]Fever: axillary temperature >38 ºC on admission, or history of fever in the past 48 hours;
[e]Hypoxia: O_2 saturations <90% on room air on admission, or supplemental O_2 requirement;
[f]Tachypnea: Age <2 months respiratory rate (RR) >60 breaths per minute (bpm); age 2-11 months RR >50 bpm; age ≥12 months RR >40 bpm;
[g]Leucocytosis: For age 1-11 months: white cell count >15 × 10^9/L; for age ≥12 months: white cell count >13 × 10^9/L;
[h] Positive Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter >6mm;
[i] Combined category of death within 30 days of hospitalization and the assumption if not mechanically ventilated then would have died

Table 8.5 Chest X-ray intrathoracic lymphadenopathy and bilateral air trapping association with clinical parameters, HIV exposure status, acute phase reactants and poor prognostic outcomes in children hospitalized with WHO-defined severe or very severe pneumonia

All Children	**Thoracic Lymph adenopathy N=135 (%)**	No Thoracic Lymph adenopathy N=723 (%)	OR (95% CI)	Adj OR* (95% CI)	**Bilateral air trapping N=131 (%)**	No Bilateral air trapping N=727 (%)	OR (95%CI)	Adj OR* (95% CI)
Female	48 (36)	356 (49)	*p*=0.004[~]	N/A	52 (40)	352 (48)	*p*=0.066[~]	N/A
Male	87 (64)	367 (51)	*p*=0.004[~]	N/A	79 (60)	375 (52)	*p*=0.066[~]	N/A
Mean Age in months	12.55	8.38	N/A	N/A	9.65	8.93	N/A	N/A
Median Age in months (IQR[+])	9 (5-16)	5 (2-11)	*p*= 0.000[#]	N/A	6 (3-13)	6 (2-12)	*p*= 0.100[#]	N/A
Age 1-5 months	43 (32)	383 (53)	0.4 (0.3-0.6)	**0.4 (0.3-0.6)**	64 (49)	362 (50)	1.0 (0.7-1.4)	1.0 (0.7-1.5)
Age 6-11 months	38 (28)	174 (24)	1.3 (0.8-1.9)	1.2 (0.8-1.9)	33 (25)	179 (25)	1.0 (0.7-1.6)	1.1 (0.7-1.7)
Age 12-59 months	54 (40)	166 (23)	2.2 (1.5-3.3)	**2.2 (1.4-3.3)**	34 (26)	186 (26)	1.0 (0.7-1.6)	0.9 (0.6-1.4)
PCV unvaccinated	16/123 (13)	167/677 (25)	0.5 (0.3-0.8)	0.6 (0.3-1.1)	20/121 (17)	163/679 (24)	0.6 (0.4-1.1)	0.6 (0.3-1.1)
PCV partially vaccinated [a]	28/123 (23)	228/677 (34)	0.6 (0.4-0.9)	0.9 (0.5-1.4)	45/121 (37)	211/679 (31)	1.3 (0.9-2.0)	1.4 (0.9-2.2)
PCV fully vaccinated [b]	79/123 (64)	282/677 (42)	2.5 (1.7-3.7)	**1.7 (1.1-2.9)**	56/121(46)	305/679 (45)	1.1 (0.7-1.6)	1.1 (0.7-1.9)
Severe Malnutrition [c]	41/134 (31)	214/718 (30)	1.0 (0.7-1.6)	1.0 (0.7-1.6)	40 (31)	215/721 (30)	1.0 (0.7-1.6)	1.0 (0.7-1.6)
Fever [d]	94 (70)	455 (63)	1.4 (0.9-2.0)	1.4 (0.9-2.2)	87 (66)	462 (64)	1.1 (0.8-1.7)	1.0 (0.7-1.5)
Hypoxia [e]	98/134 (73)	548/720 (76)	0.9 (0.6-1.3)	1.0 (0.6-1.6)	99/130 (76)	547/724 (76)	1.0 (0.7-1.6)	1.0 (0.6-1.5)
Tachypnea [f]	109/134 (81)	545/706 (77)	1.3 (0.8-2.1)	1.3 (0.8-2.2)	109/130 (84)	545/710 (77)	1.6 (0.9-2.5)	1.5 (0.9-2.6)
Crackles	92/134 (69)	465/708 (66)	1.1 (0.8-1.7)	1.1 (0.7-1.6)	79/129 (61)	478/713 (67)	0.8 (0.5-1.1)	0.8 (0.6-1.3)
Wheezing	53/134 (40)	217/705 (31)	1.5 (1.0-2.1)	1.4 (0.9-2.1)	58/128 (45)	212/711(30)	2.0 (1.3-2.9)	**2.3 (1.5-3.5)**

HIV-unexposed	68/127 (54)	360/693 (52)	1.1 (0.7-1.6)	1.1 (0.7-1.6)	60/123 (49)	368/697 (53)	0.9 (0.6-1.2)	0.8 (0.6-1.2)
HIV-exposed uninfected (HEU)	41/127 (33)	243/693 (35)	0.9 (0.6-1.3)	0.9 (0.6-1.4)	42/123 (34)	242/697 (35)	1.0 (0.7-1.5)	1.0 (0.7-1.5)
HIV-infected	18/127 (14)	90/693 (13)	1.1 (0.6-1.9)	1.1 (0.6-1.9)	21/123 (17)	87/697 (12)	1.4 (0.9-2.4)	1.5 (0.9-2.6)
Raised CRP ≥40 mg/dL	31/130 (24)	196/715 (27)	0.8 (0.5-1.3)	0.7 (0.4-1.1)	23 (18)	204/714 (29)	0.5 (0.3-0.9)	**0.5 (0.3-0.9)**
Leucocytosis [g]	60/133 (45)	331/721 (46)	1.0 (0.7-1.4)	0.8 (0.6-1.2)	61(47)	330/723 (46)	1.0 (0.7-1.5)	0.9 (0.6-1.3)
Positive Antibiotic serum activity [h]	64/128 (50)	344/690 (50)	1.0 (0.7-1.5)	1.0 (0.6-1.4)	60/125 (48)	348/693 (50)	0.9 (0.6-1.3)	0.9 (0.6-1.3)
Hospital stay ≥3 days	123(91)	664 (92)	0.9 (0.5-1.7)	1.1 (0.5-2.1)	118 (90)	669 (92)	0.8 (0.4-1.5)	0.8 (0.4-1.5)
Mechanical Ventilation	2 (1)	68 (9)	0.1 (0-0.6)	**0.2 (0.0-0.8)**	6 (5)	64 (9)	0.5 (0.2-1.2)	0.6 (0.2-1.3)
Death within 30 days hospitalization	3/121^ (2)	41/610^ (7)	0.4 (0.1-1.2)	0.2 (0.1-1.4)	4/111^ (4)	40/620^ (6)	0.5 (0.2-1.5)	0.5 (0.2-1.8)
Mechanical ventilation or death[i]	5/121^ (4)	96/622^ (15)	0.2 (0.1-0.6)	**0.2 (0.1-0.7)**	10/112 ^ (9)	91/631^ (14)	0.6 (0.3-1.2)	0.6 (0.2-1.1)

*Adjusted odds ratio using a multiple logistic regression model: adjusting for age, HIV exposure status, severe malnutrition, hypoxia, tachypnea and wheeze;
[+] IQR Interquartile range;
N/A not applicale;
[~] *p* value calculated using Pearson's chi-squared test;
[#] *p* value calculated using Wilcoxon rank sum test for non-parametric data;
[^] some children were lost to follow up within the 30 day period of initial hospitalization;
[a]PCV partially vaccinated: Vaccination status based on the number of doses a child received and their age at first dose or age at vaccine introduction;
[b]PCV fully vaccinated: defined as 3 or more doses, or 2 or more doses for a child aged 12 to 24 months at either first dose of vaccine or at vaccine introduction, or 1 or more doses for a child aged 24 months or older at either first dose of vaccine or at vaccine introduction;
[c]Severe Malnutrition: Weight-for-age less than -3 z-scores below the median of the WHO child growth standards;
[d]Fever: axillary temperature >38 ºC on admission, or history of fever in the past 48 hours;
[e]Hypoxia: O_2 saturations <90% on room air on admission, or supplemental O_2 requirement;
[f]Tachypnea: Age <2 months respiratory rate (RR) >60 breaths per minute (bpm); age 2-11 months RR >50 bpm; age ≥12 months RR >40 bpm;
[g]Leucocytosis: For age 1-11 months: white cell count >15 × 10^9/L; for age ≥12 months: white cell count >13 × 10^9/L;
[h] Positive Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter >6mm;
[i] Combined category of death within 30 days of hospitalization and the assumption if not mechanically ventilated then would have died

Table 8.6 Chest X-ray patterns of chronic lung disease and Normal chest X-ray association with clinical parameters, HIV exposure status, acute phase reactants and poor prognostic outcomes in children hospitalized with WHO-defined severe or very severe pneumonia

All Children	**Chronic Lung disease** N=14 (%)	No Chronic Lung disease N=844 (%)	OR (95% CI)	Adj OR* (95% CI)	**Normal CXR** **N=219 (%)**	Any CXR Changes N=639 (%)	OR (95% CI)	Adj OR* (95% CI)
Female	5 (36)	399 (47)	*p*=0.390~	N/A	90 (41)	314 (49)	*p*=0.040~	N/A
Male	9 (64)	445 (53)	*p*=0.390~	N/A	129 (59)	325 (51)	*p*=0.040~	N/A
Mean Age in months	16.86	8.91	N/A	N/A	7.68	9.50	N/A	N/A
Median Age in months (IQR+)	13.5 (4-23)	6 (2-12)	*p*=0.050	N/A	4 (2-11)	6 (3-13)	*p*=0.000	N/A
Age 1-5 months	5 (36)	421 (50)	0.6 (0.2-1.7)	0.6 (0.2-1.8)	125 (57)	301 (47)	1.4 (1.1-2.0)	**1.6 (1.1-2.2)**
Age 6-11 months	1 (7)	211 (25)	0.2 (0-1.7)	0.2 (0-1.4)	44 (20)	168 (26)	0.7 (0.5-1.0)	**0.6 (0.4-1.0)**
Age 12-59 months	8 (57)	212 (25)	3.9 (1.4-11.6)	**5.2 (1.7-16.9)**	50 (23)	170 (27)	0.8 (0.6-1.2)	0.8 (0.5-1.2)
PCV unvaccinated	3/11 (27)	180/789 (23)	1.3 (0.3-4.8)	1.8 (0.4-7.5)	54/203 (27)	129/597 (22)	1.3 (0.9-1.9)	1.1 (0.7-1.7)
PCV partially vaccinated [a]	4/11(36)	252/789 (32)	1.2 (0.4-4.2)	2.4 (0.6-10.4)	68/203 (34)	188/597 (31)	1.1 (0.8-1.6)	0.9 (0.6-1.4)
PCV fully vaccinated [b]	4/11(36)	357/789 (45)	0.7 (0.2-2.4)	0.3 (0.1-1.1)	81/203 (40)	280/597 (47)	0.8 (0.5-1.1)	1.0 (0.6-1.5)
Severe Malnutrition [c]	9 (64)	246/838 (29)	4.3 (1.4-13.1)	**3.9 (1.2-12.6)**	45 (21)	210/633 (33)	0.5 (0.4-0.8)	**0.6 (0.4-0.9)**
Fever [d]	9 (64)	540 (64)	1.0 (0.3-3.1)	0.8 (0.3-2.5)	108 (49)	441 (69)	0.4 (0.3-0.6)	**0.5 (0.3-0.6)**
Hypoxia [e]	11 (79)	635/840 (76)	1.2 (0.3-4.3)	1.7 (0.4-6.4)	169/218 (76)	477/636 (75)	1.1 (0.8-1.7)	1.0 (0.7-1.5)
Tachypnea [f]	10 (71)	644/826 (78)	0.7 (0.2-2.3)	0.6 (0.2-1.9)	154/213 (72)	500/627 (80)	0.7 (0.5-0.9)	**0.6 (0.4-0.9)**
Crackles	9/13 (69)	548/829 (66)	1.2 (0.4-3.8)	0.9 (0.3-3.2)	138/217 (64)	419/625 (67)	0.9 (0.6-1.2)	0.8 (0.6-1.2)
Wheezing	4/13 (31)	266/826 (32)	0.9 (0.3-3.1)	1.1 (0.3-3.9)	86/217 (40)	184/622 (30)	1.6 (1.1-2.2)	1.3 (0.9-1.9)

HIV-unexposed	5 (36)	423/806 (52)	0.5 (0.2-1.5)	0.7 (0.2-2.1)	123/211 (59)	305/609 (50)	1.4 (1.0-1.9)	**1.3 (1.0-1.8)**
HIV-exposed uninfected (HEU)	4 (29)	280/806 (35)	0.8 (0.2-2.4)	0.8 (0.2-2.6)	81/211 (39)	203/609 (33)	1.2 (0.9-1.7)	1.3 (0.9-1.8)
HIV-infected	5 (36)	103/806 (13)	3.8 (1.2-11.5)	2.2 (0.7-.7.7)	7/211 (3)	101/609 (17)	0.2 (0.1-0.4)	**0.2 (0.1-0.4)**
Raised CRP ≥40 mg/dL	8 (47)	219/831 (26)	3.7 (1.2-10.9)	2.5 (0.8-7.7)	39/216 (18)	188/629 (30)	0.5 (0.4-0.8)	**0.6 (0.4-0.9)**
Leucocytosis [g]	7(50)	384/840 (46)	1.2 (0.4-3.4)	1.0 (0.4-3.1)	93/219 (42)	298/635 (47)	0.8 (0.6-1.1)	1.0 (0.7-1.4)
Positive Antibiotic serum activity [h]	8 (57)	400/804 (50)	1.3 (0.5-3.9)	1.4 (0.5-4.2)	87/209 (42)	321/609 (53)	0.6 (0.5-0.9)	**0.6 (0.5-0.9)**
Hospital stay ≥3 days	14 (100)	773 (92)	1.0	1.0	197 (90)	590 (92)	0.7 (0.4-1.3)	0.7 (0.4-1.1)
Mechanical Ventilation	1 (7)	69 (8)	0.9 (0.1-6.7)	0.9 (0.1-7.2)	9 (4)	61 (10)	0.4 (0.2-0.8)	**0.4 (0.2-0.8)**
Death within 30 days hospitalization	1/13^ (7)	43/718^ (6)	1.3 (0.2-10.3)	0.5 (0.1-4.8)	5/193^ (3)	39/538^ (7)	0.3 (0.1-0.9)	0.5 (0.2-1.4)
Mechanical ventilation or death[i]	2/14^ (14)	99/729^ (14)	1.1 (0.2-4.8)	0.7 (0.1-3.4)	13/193^ (7)	88/550^ (16)	0.4 (0.2-0.7)	**0.4 (0.2-0.8)**

*Adjusted odds ratio using a multiple logistic regression model: adjusting for age, HIV exposure status, severe malnutrition, hypoxia, tachypnea and wheeze;
[+] IQR Interquartile range;
N/A not applicable;
[~] *p* value calculated using Pearson's chi-squared test;
[#] *p* value calculated using Wilcoxon rank sum test for non-parametric data;
[^] some children were lost to follow up within the 30 day period of initial hospitalization;
[a]PCV partially vaccinated: Vaccination status based on the number of doses a child received and their age at first dose or age at vaccine introduction;
[b]PCV fully vaccinated: defined as 3 or more doses, or 2 or more doses for a child aged 12 to 24 months at either first dose of vaccine or at vaccine introduction, or 1 or more doses for a child aged 24 months or older at either first dose of vaccine or at vaccine introduction;
[c]Severe Malnutrition: Weight-for-age less than -3 z-scores below the median of the WHO child growth standards;
[d]Fever: axillary temperature >38 ºC on admission, or history of fever in the past 48 hours;
[e]Hypoxia: O_2 saturations <90% on room air on admission, or supplemental O_2 requirement;
[f]Tachypnea: Age <2 months respiratory rate (RR) >60 breaths per minute (bpm); age 2-11 months RR >50 bpm; age ≥12 months RR >40 bpm;
[g]Leucocytosis: For age 1-11 months: white cell count $>15 \times 10^9$/L; for age ≥12 months: white cell count $>13 \times 10^9$/L;
[h] Positive Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter >6mm;
[i] Combined category of death within 30 days of hospitalization and the assumption if not mechanically ventilated then would have died

8.1.8 Sensitivity and specificity of clinical history, clinical findings, acute phase reactants and poor clinical prognostic outcomes in predicting CXR-PEP compared to cases without CXR-PEP in HIV-unexposed, HIV-exposed, uninfected and HIV-infected children hospitalized with WHO-defined severe or very severe pneumonia

On clinical history, PCV vaccination status was poorly predictive of whether or not the cases had CXR-PEP, positive predictive values of 29%-34% and negative predictive values of 59%-65% in all 3 HIV-exposure groups; refer Table 8.7.

The clinical finding of fever was a reasonable clinical predictor of CXR-PEP with sensitivities of 73%, 66% and 75% in HIV-unexposed, HEU and HIV-infected children, respectively, but considerably lower specificity (ranging from 23 to 45%, lowest in HIV-infected children), Table 6.4. The absence of fever was a reasonable predictor of not having CXR-PEP in HIV-unexposed children (negative predictive value 73% (95% CI, 66-80%). A similar trend of high sensitivity but lower specificity in predicting CXR-PEP was found for other clinical findings including hypoxia, tachypnea and crackles, refer Table 8.7.

In contrast CRP $\geq$40 mg/dL was a poor a predictor of CXR-PEP with sensitivity ranging from 35%-43% and positive predictive value between 47% - 69%, in all 3 HIV groups. However the absence of CRP $\geq$40 mg/dL was a good predictor of the absence of CXR-PEP with a high specificity (72%-85%) regardless of HIV group, and high negative predictive value in HIV-unexposed (71%) and HEU (71%) children. Similarly, the presence of leucocytosis and positive antibiotic serum activity had low sensitivity for predicting CXR-PEP (46%-58%) and (48%-57%) respectively in all 3 HIV groups, with low specificity, low positive and negative predictive values; refer Table 8.7.

Table 8.7 Sensitivity and specificity of clinical findings, acute phase reactants and poor clinical outcomes in predicting Chest X-Ray Primary End-Point Pneumonia (CXR-PEP) in HIV-unexposed, HIV-exposed uninfected and HIV-infected children hospitalized with WHO-defined severe or very severe pneumonia

Clinical	**HIV-unexposed (n=428); CXR-PEP**				**HEU (n=284); CXR-PEP**				**HIV-infected (n=108); CXR-PEP**			
	% Sensitivity (95% CI)	% Specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)	% Sensitivity (95% CI)	% Specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)	% Sensitivity (95% CI)	% Specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)
PCV fully Vaccinated [a]	43(35-51)	49(43-56)	34(27-41)	59(52-65)	38(28-49)	56(48-64)	29(21-39)	65(57-73)	38(28-49)	56(48-64)	29(21-39)	65(57-73)
Severe Malnutrition [b]	28(21-36)	82(77-86)	48(38-59)	65(60-70)	48(38-59)	75(68-81)	49(38-60)	75(68-81)	52(39-64)	49(33-65)	60(46-73)	40(27-55)
Fever [c]	**73(66-80)**	**45(39-51)**	**45(39-51)**	73(66-80)	**66(56-75)**	**42(34-48)**	**36(29-43)**	71(62-79)	**75(63-85)**	**23(12-39)**	**60(48-70)**	39(20-59)
Hypoxia [d]	76(69-82)	22(17-28)	38(32-43)	60(49-70)	78(68-86)	31(24-38)	36(29-43)	73(62-83)	75(63-82)	16(7-31)	58(46-68)	30(13-53)
Tachypnea [e]	**80(73-86)**	19(14-24)	38(32-43)	61(50-72)	77(67-85)	25(19-32)	34(27-41)	69(57-80)	75(63-85)	24(12-40)	60(48-71)	39(20-59)
Crackles	74(67-81)	32(27-38)	40(34-46)	67(58-75)	59(49-70)	41(34-49)	33(26-41)	68(58-76)	66(53-74)	33(20-50)	61(48-72)	39(23-57)
Wheezing	28(21-36)	56(49-62)	28(21-35)	56(50-62)	17(10-26)	65(58-72)	19(11-29)	62(55-68)	11 (4-21)	76 (60-88)	41(18-67)	35(25-46)
Raised CRP $\geq$40 mg/dL	**43(35-51)**	**85(80-89)**	63(53-72)	71(65-76)	**35(25-45)**	**81(74-86)**	47(34-59)	71(65-78)	**42(30-55)**	**72(56-85)**	69(52-83)	46(34-58)
Leucocytosis [f]	46(38-54)	58(52-64)	41(33-48)	64(57-70)	47(36-57)	56(49-64)	35(26-44)	68(60-75)	58(45-70)	48(32-64)	63(49-75)	43(28-58)
Positive Antibiotic serum activity[g]	57(49-65)	56(49-62)	44(37-51)	68(61-74)	56(45-67)	55(47-62)	38(29-47)	72(64-79)	48(35-62)	33(19-49)	50(37-63)	31(18-47)

[a]PCV fully vaccinated: defined as 3 or more doses, or 2 or more doses for a child aged 12 to 24 months at either first dose of vaccine or at vaccine introduction, or 1 or more doses for a child aged 24 months or older at either first dose of vaccine or at vaccine introduction;
[b]Severe Malnutrition: Weight-for-age less than -3 z-scores below the median of the WHO child growth standards;
[c]Fever: axillary temperature >38 ºC on admission, or history of fever in the past 48 hours;
[d]Hypoxia: O_2 saturations <90% on room air on admission, or supplemental O_2 requirement;
[e]Tachypnea: Age <2 months respiratory rate (RR) >60 breaths per minute (bpm); age 2-11 months RR >50 bpm; age $\geq$12 months RR >40 bpm
[f]Leucocytosis: For age 1-11 months: white cell count >15 × 10^9/L; for age $\geq$12 months: white cell count >13 × 10^9/L;
[g] Positive Antibiotic serum activity: Positive if serum antibiotic activity zone of inhibition diameter >6mm;

8.2 Discussion: Objective 3

In children hospitalized with WHO-defined severe or very severe pneumonia, using a multivariate analyses model adjusting for age, HIV exposure status and clinical parameters, features independently associated with presence of CXR-PEP (which is considered as a surrogate for bacterial infection), included presence of severe malnutrition, fever and CRP $\geq$ 40mg/dL. The clinical finding of fever being independently predictive of CXR-PEP, including having a high sensitivity (66%-75%) but low specificity (23%-45%) is consistent with the literature (70, 71, 73-75). The observation of severe malnutrition corroborates with the notion that malnourished children are predisposed to developing bacterial CAP (57, 58, 66). The presence of CXR-PEP was also associated with a greater need for mechanical ventilation and also the composite outcome of mechanical ventilation or death.

However there was no single clinical or laboratory parameter that had both high sensitivity and specificity to discriminate between CXR-PEP from non CXR-PEP cases, regardless of HIV exposure status. These findings are consistent with the findings of a recent meta-analysis by Rambaud-Althaus *et al.* A significant limitation of this meta-analysis was the lack of standardized chest X-ray reporting (82).

Children with CXR-PEP compared to cases without CXR-PEP were less likely to be fully vaccinated with PCV. This supports the literature that the introduction of PCV demonstrated a VE based on WHO standardized interpretation criteria for CXR-PEP (15) of 20% in HIV-uninfected South African children and 13% in HIV-infected South African children not on ART (16), 37% in Gambian children (17), 30% in children in the USA (18) and 23% in Philippino children (19).

Conversely among children with WHO-defined severe or very severe pneumonia, cases in whom the chest X-ray was evaluated as being normal were less likely to present with fever,

tachypnea or to have CRP ≥40mg/dL. Furthermore, cases with a normal chest X-ray were also less likely to require mechanical ventilation or fulfil the composite outcome of mechanical ventilation or death.

We found that CXR-PEP was not associated with the clinical finding of tachypnea in the multivariate analyses. However tachypnea had the highest sensitivity for predicting CXR-PEP in HIV-unexposed children, albeit having low specificity. Conversely a normal chest X-ray was less likely to be associated with tachypnea. This is consistent with the recent meta-analysis by Rambaud-Althaus *et al* who despite finding that tachypnea was the best individual clinical predictor for chest X-ray confirmed pneumonia, the pooled sensitivity was only 79% and pooled specificity only 31%, indicating that presence of tachypnea was of poor diagnostic value for predicting chest X-ray confirmed pneumonia (82).

This is consistent with other literature that found tachypnea to be a poor predictor of chest X-ray confirmed pneumonia (71-74, 77, 78), with the sensitivity of chest X-ray for predicting tachypnea wide; ranging from 13%-74%; with better specificity between 67%-95% (71-73, 78). Variability in the clinical definition of tachypnea and lack of standardized reporting in the definition of "chest X-ray pneumonia" in the different studies could explain these observed differences.

Children with CXR-PEP were less likely to present with wheezing. Consistently in all 3 HIV groups, wheezing was associated with absence of CXR-PEP with a specificity of (56%-76%), negative predictive value (35%-62%), sensitivity of (11%-28%) and positive predictive value of (19%-41%). Our results are consistent with the meta-analysis by Rambaud-Althaus *et al* which demonstrated a high pooled specificity of 75%, and low pooled sensitivity of 22% of wheezing for chest X-ray confirmed pneumonia (82). Furthermore children with bilateral air trapping on chest X-ray were more likely to have wheezing compared to children without

bilateral air trapping on the multivariate analysis. Hence wheezing may be a useful surrogate for non-bacterial pneumonia, even in the context of a study such as ours where we excluded children presenting with severe pneumonia and wheezing who responded to a trial of bronchodilator nebulizations.

Our findings of CRP ≥40mg/dL being independently predictive of CXR-PEP, whilst children with other infiltrate only and normal chest X-rays were less likely to have elevated CRP, is also consistent with other studies (63, 65, 68, 69). However, although raised CRP ≥40mg/dL had a good specificity (72%-85%) for excluding CXR-PEP, it had a low sensitivity (35%-43%). This corroborates a study by Lala *et al* who found that although a raised CRP levels may be useful in the clinical setting, a raised CRP could not be a reliable surrogate for bacterial pneumonia, as this acute phase reactant did not differentiate from bacteraemic or respiratory viral infection in both HIV-uninfected and HIV-infected children with clinical pneumonia (158).

The presence of CXR-PEP was also associated with a greater need for mechanical ventilation and also the composite outcome of mechanical ventilation or death. Conversely cases with a normal chest X-ray were less likely to require mechanical ventilation or fulfil the composite outcome of mechanical ventilation or death. This is consistent with previous findings that children with air space consolidation had higher odds for poorer clinical outcomes, including mechanical ventilation, compared to those with less extensive lung changes on chest X-ray (66, 83). Although we did not demonstrate an association between CXR-PEP and case fatality within 30 days of hospitalization, which could be due to insufficient power to evaluate for this association in our study, and also the availability of mechanical ventilation which likely mitigated against more deaths. This is corroborated by the finding of cases with CXR-PEP being more likely to have the composite outcome of mechanical ventilation or death within 30 days of admission.

The different epidemiological settings of childhood pneumonia described in the literature including differences with regards to HIV prevalence, median age of children included in different studies, national immunization programs for HiBCV and PCV vaccines, malnutrition prevalence, disease severity, timing of hospitalization, and prior antibiotic usage; all of which are important factors to consider when comparing our study to the literature (60-62, 104, 122, 153).

The lack of standardization of clinical definitions and poor inter observer agreement amongst clinicians for certain clinical symptoms and signs (82) is also important to consider when comparing our findings to the literature.

The lack of standardized reporting in the definition of "chest X-ray pneumonia" in other studies is also very important, as a number of studies did not differentiate in their methodology between air space/alveolar consolidation and interstitial infiltrate on chest X-ray (71, 73, 77-81). There is also significant variability in the application of WHO standardized chest X-ray reporting in the literature. Hence direct comparisons between these studies to our study findings need to be interpreted with caution.

8.3 Limitations: Objective 3

The clinical definition of hypoxia used in this study had variability; children in this study that were put on oxygen shortly after admission were missing room air oxygen saturation. Hence the coding used for the hypoxia variable automatically considers these children on supplemental oxygen on admission as hypoxic; but they may not have all had "true hypoxemia on admission".

We did not demonstrate an association between CXR-PEP and the poorer prognostic clinical outcome of case fatality within 30 days of hospitalization in this study. From the 731 children with available follow up results, a low percentage 44 (6%) had death within 30 days of hospitalization, similar to the findings by Kelly *et al* (66). Hence like this study we did not have sufficient power to evaluate for an association between CXR-PEP and mortality within 30 days of hospitalization in the multivariate analyses.

9 Objective 4: Chest X-ray Pattern Association with Microbiological Etiology: Results, Discussions, Limitations

Objective: To determine the association of specific chest X-ray patterns with the PERCH Quantitative Analysis (PQA) model predicted high probability of bacterial, respiratory virus and *Pneumocystis jiroveci* associated pneumonia, microbiologically confirmed pneumococcal pneumonia (MCPP), culture confirmed pulmonary TB and culture or clinically confirmed pulmonary TB in HIV-unexposed, HEU and HIV-infected children hospitalized with WHO-defined severe or very severe community acquired pneumonia.

9.1 Summary of Methods

The PQA model is described in detail in the methods of this PhD thesis. Briefly the PQA model is a partially latent class model (PLCM) analysis, that was developed as a "statistical probabilistic approach to incorporate data from a variety of specimens and tests from both cases and controls to produce an etiology pie for pneumonia" (148). "The analysis integrates data from multiple types of measurements, including both case-only and case-control measurements, and accounts for varying measurement error rates to estimate the distribution of pathogens among the cases". The PQA model estimates the attributable probability of disease for each of the investigated pathogens, producing both a probability of attribution at an individual and population level (148, 149).

For the purposes of this analysis, the PQA model was programmed to perform 10,000 iterations on data from cases with interpretable chest X-rays using the R version 3.1.0 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). The model generated a probability index for each of the 33 organisms with the sum of the probability indices for the 33 pathogens adding to 1.0 for each individual case.

9.2 Results:

As described in detail in this PhD thesis, during the two year study period 920 cases with WHO-defined clinical severe or very severe pneumonia were enrolled. Chest X-rays were available in 885 (96%) cases. Of these 27 (3%) were uninterpretable based on the 3 reader consensus reading. From the 858 children with interpretable chest X-rays, 428 (50%) were HIV-unexposed, 284 (33%) were HEU, 108 (13%) HIV-infected and 38 (4%) HIV-unknown exposure, uninfected.

9.2.1 Etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB for each HIV exposure group

HIV-unexposed children had a prevalence of 11%, 6 % and 4% for bacterial etiology based on a PQA model probability index $\geq$ 0.5, $\geq$ 0.6 and $\geq$ 0.7, respectively. This was in comparison to a higher prevalence of respiratory viral etiology of 44%, using a PQA model probability index $\geq$ 0.5. MCCP was prevalent in 6% of HIV-unexposed children. Culture confirmed PTB was prevalent in 3%, and culture or clinically confirmed PTB in 13% of HIV-unexposed children. Refer Table 9.1.

HIV-exposed uninfected (HEU) children had a prevalence of 4%, 3% and 3% for bacterial etiology based on a PQA model probability index $\geq$ 0.5, $\geq$ 0.6 and $\geq$ 0.7, respectively. This was in comparison to a higher prevalence of respiratory viral etiology of 38%, based on a PQA model probability index $\geq$ 0.5. *Pneumocystis jiroveci* etiology had a prevalence of 3% in HEU children, based on a PQA model probability index $\geq$ 0.5. Culture confirmed PTB was prevalent in 4%, and culture or clinically confirmed PTB in 13% of HEU children. Refer Table 9.1.

HIV-infected children had a prevalence of 22%, 10% and 6% for bacterial etiology based on a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7, respectively. Similarly, respiratory viral etiology had a prevalence of 20%, using a PQA model probability index ≥ 0.5 and *Pneumocystis jiroveci* etiology had a prevalence of 21% of HIV-infected children. Culture confirmed PTB was prevalent in 3%, and culture or clinically confirmed PTB in 42% of HIV-infected children. Refer Table 9.1.

Table 9.1 Microbiological Etiology in Children hospitalized for WHO-defined severe or very severe pneumonia based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

Microbiological etiology	**HIV-Unexposed** **N=428 (%)**	**HEU** **N=284 (%)**	**HIV-infected** **N=108 (%)**
PQA* model probability index ≥ 0.5 for bacterial etiology	46 (11)	10 (4)	24 (22)
PQA* model probability index ≥ 0.6 for bacterial etiology	27 (6)	9 (3)	11 (10)
PQA* model probability index ≥ 0.7 for bacterial etiology	15 (4)	8 (3)	6 (6)
MCCP [#]	27 (6)	18 (6)	13 (12)
PQA* model probability index ≥ 0.5 for Respiratory Viral etiology	189 (44)	107 (38)	22 (20)
PQA model probability index ≥ 0.5 *Pneumocystis jiroveci* etiology	N/A	9 (3)	23 (21)
Culture Confirmed Pulmonary TB	12 (3)	12 (4)	3 (3)
Culture or clinically confirmed pulmonary TB	54 (13)	36 (13)	45 (42)

[*] PQA - PERCH Quantitative Analysis
[#] Microbiologically Confirmed Pneumococcal Pneumonia
N/A: not applicable

9.2.2 Chest X-Ray Primary End Point Pneumonia (CXR-PEP) association with microbiological etiology

HIV-unexposed children with a PQA model probability index ≥ 0.5 for bacterial etiology had a 2.1 fold (95% CI 1.1-4.1) higher odds of CXR-PEP (15%) compared to non CXR-PEP (8%, *p*= 0.018). Using a higher PQA model probability index ≥ 0.6 (8% vs 5%) and ≥ 0.7 (4% vs 3%) for bacterial etiology was not, however, associated with presence of CXR-PEP compared to non CXR-PEP cases, albeit with smaller number of cases available for this analysis. Similarly HIV-unexposed children with MCPP had a 3.0 fold (95% CI 1.3-6.7) higher odds of CXR-PEP (11%) compared to non CXR-PEP (4%, *p*=0.008). Refer Table 9.2.

Among HIV-unexposed children with a PQA model probability index ≥ 0.5 for respiratory viral etiology, there was a similar percentage of cases with CXR-PEP (50%) compared to non CXR-PEP (40%, OR 1.3; 95% CI 0.9-2.0). Furthermore HIV-unexposed children with culture confirmed PTB (4% vs 2%) and culture or clinically confirmed PTB (14% vs 12%) demonstrated no significant differences for the presence of CXR-PEP compared to non CXR-PEP cases.

Among HEU children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology there was no difference in the prevalence of CXR-PEP compared to non CXR-PEP cases (3% vs 4%), (3% vs 3%) and (3% vs 3%), respectively. Furthermore HEU with a PQA model probability index ≥ 0.5 for respiratory viral etiology (37% vs 38%), PQA model probability index ≥ 0.5 for *Pneumocystis jiroveci* etiology (4% vs 3%), MCCP (6% vs 6%), culture confirmed PTB (6% vs 3%) and culture or clinically diagnosed PTB (15% vs 12%) demonstrated no significant difference for CXR-PEP compared to non CXR-PEP. Refer Table 9.2.

Although not significant HIV-infected children with a PQA model probability index ≥ 0.5 for respiratory viral etiology and PQA model probability index ≥ 0.5 for *Pneumocystis jiroveci* etiology trended to have a greater odds for CXR-PEP vs non CXR-PEP (25% vs 14%; OR 2.0; 95% CI 0.7-5.6) and (26% vs 14%, OR 2.2; 95% CI 0.8-6.1), respectively. HIV-infected children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology did not differ in prevalence of CXR-PEP compared to non CXR-PEP cases (23% vs 21%), (8% vs 14%) and (5% vs 7%) respectively. Similarly HIV-infected children with culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of CXR-PEP compared to non CXR-PEP cases (3% vs 3%) and (43% vs 40%), respectively. Refer Table 9.2.

9.2.3 Sensitivity, Specificity of CXR-PEP in predicting microbiological etiology based on PERCH Quantitative Analysis model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed PTB

In HIV-unexposed children the sensitivity of CXR-PEP in predicting PQA model probability index ≥ 0.5 for bacterial etiology was low 54% (95% CI 39%-69%), with a low positive predictive value 15% (95% CI 10%-22%), but with higher specificity 64% (95% CI 59%-69%) and a high negative predictive value of 92% (95% CI 88%-95%).

Similarly in HIV-unexposed children, the sensitivity of CXR-PEP in predicting PQA model probability index ≥ 0.6 and ≥ 0.7 for bacterial etiology was low 48% (95% CI 29%-68%) and 40% (95% CI 16%-68%), respectively. There was a low positive predictive value 8% (95% CI 4%-13%) and 4% (95% CI 1%-8%), respectively, but with higher specificity 63% (95% CI 58%-67%) and 62% (95% CI 57%-67%), respectively and a very high negative predictive value 95% (95% CI 91%-97%) and 97% (95% CI 94%-98%), respectively. Refer Table 9.3.

Similarly in HIV-unexposed children the sensitivity of CXR-PEP in predicting MCPP was low 63% (95% CI 42%-81%), with a low positive predictive value of 11% (95% CI 6%-16%), low specificity of 64% (95% CI 59%-68%) but with a high negative predictive value of 96% (95% CI 93%-98%). Refer Table 9.3.

In HIV-unexposed children the sensitivity of CXR-PEP in predicting culture confirmed PTB was low 58% (95% CI 28%-85%), specificity 63% (95% CI 58%-67%), with a very low positive predictive value of 4% (95% CI 2%-9%) and a very high negative predictive value of 98% (95% CI 96%-99%). In HIV-unexposed children the sensitivity of CXR-PEP in predicting culture or clinically PTB was lower 43% (95% CI 29%-57%), with unchanged specificity of 63% (95% CI 57%-68%), improved positive predictive value of 14% (95% CI 9%-20%), but lower negative predictive value of 88% (95% CI 84%-92%). Refer Table 9.3.

In HEU children the sensitivity of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for bacterial etiology was low 30% (95% CI 7%-65%), with a low positive predictive value 3% (95% CI 1%-9%), but with higher specificity 67% (95% CI 61%-72%) and a high negative predictive value of 96% (95% CI 92%-99%). Similarly the sensitivity of CXR-PEP in predicting MCPP was low 33% (95% CI 13-59), with a very low positive predictive value of 7% (95% CI 2%-13%), low specificity of 67% (95% CI 61%-73%), but with a high negative predictive value of 94% (95% CI 89%-97%). Refer Table 9.3.

In HIV-infected children the sensitivity of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for bacterial etiology was improved 63% (95% CI 41%-82%), with a low positive predictive value 23% (95% CI 14%-35%), low specificity 41% (95% CI 30%-52%) and a lower negative predictive value of 79% (95% CI 64%-90%). Similarly the sensitivity of CXR-PEP in predicting MCPP was 77% (95% CI 46%-95%), with a low positive predictive

value of 15% (95% CI 8%-27%), low specificity of 42% (95% CI 32%-53%), but with a high negative predictive value of 93% (95% CI 81%-99%). Refer Table 9.3.

In HIV-infected children the sensitivity of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for respiratory viral etiology was high 73% (95% CI 50%-89%), with a positive predictive value of 25% (95% CI 15%-37%), a lower specificity of 43% (95% CI 32%-54%) and a higher negative predictive value of 86% (95% CI 72%-95%). Similarly the sensitivity of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for *Pneumocystis jiroveci* etiology was high 74% (95% CI 52%-90%), with a positive predictive value of 26% (95% CI 16%-39%), with a lower specificity of 44% (95% CI 33%-55%) and a higher negative predictive value of 86% (95% CI 72%-95%). Refer Table 9.3.

Table 9.2 Chest X-Ray primary end point pneumonia (CXR-PEP) association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

	HIV-unexposed (N=428)			**HEU** (N=284)			**HIV-infected** (N=108)		
Microbiological etiology	**CXR-PEP** N=163 (%)	No CXR-PEP N=265 (%)	OR (95% CI)	**CXR-PEP** N=94 (%)	No CXR-PEP N=190 (%)	OR (95% CI)	**CXR-PEP** N=65 (%)	No CXR-PEP N=43 (%)	OR (95% CI)
PQA* model probability index ≥ 0.5 for bacterial etiology	25 (15)	21 (8)	**2.1 (1.1-3.9)**	3 (3)	7 (4)	0.9 (0.2-3.4)	15 (23)	9 (21)	1.1 (0.4-2.9)
PQA* model probability index ≥ 0.6 for bacterial etiology	13 (8)	14 (5)	1.6 (0.7-3.4)	3 (3)	6 (3)	1.0 (0.2-4.1)	5 (8)	6 (14)	0.5 (0.1-1.8)
PQA* model probability index ≥ 0.7 for bacterial etiology	6 (4)	9 (3)	1.1 (0.4-3.1)	3 (3)	5 (3)	1.2 (0.3-5.2)	3 (5)	3 (7)	0.6 (0.1-3.4)
MCCP #	17 (11)	10 (4)	**3.0 (1.3-6.7)**	6 (6)	12 (6)	1.0 (0.4-2.8)	10 (15)	3 (7)	**2.4 (0.6-9.4)**
PQA* model probability index ≥ 0.5 for Respiratory Viral etiology	82 (50)	107 (40)	1.3 (0.9-2.0)	35 (37)	72 (38)	0.9 (0.5-1.5)	16 (25)	6 (14)	**2.0 (0.7-5.6)**
PQA model probability index ≥ 0.5 *Pneumocystis jiroveci* etiology	N/A	N/A	N/A	4 (4)	5 (3)	1.6 (0.4-6.3)	17 (26)	6 (14)	**2.2 (0.8-6.1)**
Culture Confirmed Pulmonary TB	7 (4)	5 (2)	2.3 (0.7-7.4)	6 (6)	6/187 (3)	2.1 (0.7-6.6)	2/62 (3)	1/40 (3)	1.3 (0.1-14.8)
Culture or clinically confirmed pulmonary TB	23 (14)	31 (12)	1.2 (0.7-2.2)	14 (15)	22 (12)	1.3 (0.6-2.7)	28 (43)	17 (40)	1.2 (0.5-2.5)

*PQA - PERCH Quantitative Analysis
Microbiologically Confirmed Pneumococcal Pneumonia
N/A: not applicable

Table 9.3 Sensitivity, Specificity of CXR-PEP vs non CXR-PEP in predicting microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

	HIV-unexposed CXR-PEP				**HEU CXR-PEP**				**HIV-infected CXR-PEP**			
Micro biological etiology	% Sensitivity (95% CI)	% Specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)	% Sensitivity (95% CI)	% Specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)	% Sensitivity (95% CI)	% Specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)
PQA* model probability index $\geq$ 0.5 for bacterial etiology	54 (39-69)	64 (59-69)	15(10-22)	92 (88-95)	30 (7-65)	67(61-72)	3(1-9)	96(92-99)	63(41-82)	41(30-52)	23(14-35)	79(64-90)
PQA* model probability index $\geq$ 0.6 for bacterial etiology	48 (29-68)	63 (58-67)	8 (4-13)	95 (91-97)	33 (7-70)	67(61-72)	3(1-9)	97(93-99)	46(17-77)	38(29-47)	8 (3-17)	86(72-95)
PQA* model probability index $\geq$ 0.7 for bacterial etiology	40 (16-68)	62 (57-67)	4 (1-8)	97 (94-98)	38 (9-76)	67(61-73)	3 (1-9)	97(94-99)	50(12-88)	40(30-49)	5(1-13)	93(81-99)
MCPP[#]	63(42-81)	64(59-68)	11(6-16)	96 (93-98)	33(13-59)	67(61-73)	7(2-13)	94(89-97)	77(46-95)	42(32-53)	15(8-27)	93(81-99)
PQA* model probability index $\geq$ 0.5 for Respiratory Viral etiology	43 (36-51)	66 (60-72)	50(42-58)	60 (53-66)	33(24-43)	67(59-74)	37(28-48)	62(55-69)	73(50-89)	43(32-54)	25(15-37)	86(72-95)
PQA* model probability index $\geq$ 0.5 for PJP[^] etiology	N/A	N/A	N/A	N/A	44(14-79)	67(61-73)	4(1-11)	97(94-99)	74(52-90)	44(33-55)	26(16-39)	86(72-95)
Culture Confirmed Pulmonary TB	58 (28-85)	63(58-67)	4 (2-9)	98 (96-99)	50(21-79)	67(61-73)	6(2-13)	97(93-99)	68(9-99)	39(30-50)	3(1-11)	98(87-99)
Culture or clinically pulmonary TB	43 (29-57)	63(57-68)	14 (9-20)	88 (84-92)	39(23-57)	68(62-74)	15(8-24)	88(83-93)	62(47-76)	41(29-54)	43(31-56)	61(44-75)

9.2.4 Other Infiltrate only association with microbiological etiology

HIV-unexposed children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology did not differ in prevalence of other infiltrate only compared to no other infiltrate on chest X-ray (8% vs 10%), (5% vs 7%) and (1% vs 4%) respectively.

Similarly HIV-unexposed children with a PQA model probability index ≥ 0.5 for respiratory viral etiology (47% vs 44%), MCCP (5% vs 7%), culture confirmed PTB (0% vs 4%) and culture or clinically confirmed PTB (11% vs 13%) did not differ in prevalence of other infiltrate only compared to no other infiltrate on chest X-ray. Refer Table 9.4.

HEU children with a PQA model probability index for bacterial, respiratory viral etiology and *Pneumocystis jiroveci* etiology, MCCP, culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of other infiltrate only compared to no other infiltrate on chest X-ray. Refer Table 9.4.

HIV-infected children culture or clinically diagnosed PTB trended towards other infiltrate only compared to no other infiltrate on chest X-ray (52% vs 38%, OR 1.8; 95% CI 0.7-4.1), refer Table 9.4. HIV-infected children with culture confirmed PTB had a 14-fold higher likelihood (95% CI 1.2 -172.3; 14% vs 1%) of miliary infiltrate and children with culture or clinically confirmed PTB had a 4-fold higher likelihood (95% CI 1.2-14.5; 71% vs 37%) of miliary infiltrate on chest X-ray compared to no miliary infiltrate on chest X-ray.

Table 9.4 Other Infiltrate only association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

	HIV-unexposed (N=428)			**HEU** (N=284)			**HIV-infected** (N=108)		
Microbiological etiology	**Other infiltrate only** N=88(%)	No other infiltrate only N=340 (%)	OR (95% CI)	**Other infiltrate only** N=77(%)	No other infiltrate only N=207(%)	OR (95% CI)	**Other infiltrate only** N=29 (%)	No other infiltrate only N=79 (%)	OR (95% CI)
PQA* model probability index ≥ 0.5 for bacterial etiology	7 (8)	34 (10)	0.9 (0.4-2.1)	3 (4)	7 (3)	1.2 (0.3-4.6)	6 (21)	18 (22)	0.9 (0.3-2.5)
PQA* model probability index ≥ 0.6 for bacterial etiology	4 (5)	23 (7)	0.7 (0.2-1.9)	2 (3)	7 (3)	0.8 (0.2-3.8)	4 (14)	7 (9)	1.6 (0.4-6.1)
PQA* model probability index ≥ 0.7 for bacterial etiology	1 (1)	14 (4)	0.3 (0.1-2.1)	2 (3)	6 (3)	0.9 (0.2-4.5)	2 (7)	4 (5)	1.4 (0.2-8.0)
MCCP [#]	4 (5)	23 (7)	0.7 (0.2-1.9)	5 (6)	13 (6)	1.0 (0.4-3.0)	3 (10)	10 (13)	0.8 (0.2-3.1)
PQA* model probability index ≥ 0.5 for Respiratory Viral etiology	41 (47)	148 (44)	1.1 (0.7-1.8)	34 (44)	73 (35)	1.5 (0.9-2.5)	4 (14)	18 (23)	0.5 (0.2-1.8)
PQA model probability index ≥ 0.5 *Pneumocystis jiroveci* etiology	N/A	N/A	N/A	4 (5)	5 (3)	2.2 (0.6-8.5)	5 (17)	18 (23)	0.7 (0.2-2.1)
Culture Confirmed Pulmonary TB	0 (0)	12 (4)	1.0	3 (4)	9/204 (4)	0.9 (0.2-3.3)	1/27 (4)	2/75 (3)	1.4 (0.1-16.1)
Culture or clinically confirmed pulmonary TB	10 (11)	44 (13)	0.9 (0.4-1.8)	13 (17)	23 (11)	1.6 (0.8-3.4)	15 (52)	30 (38)	1.8 (0.7-4.1)

[*]PQA - PERCH Quantitative Analysis

[#] Microbiologically Confirmed Pneumococcal Pneumonia

N/A: not applicable

9.2.5 Thoracic lymphadenopathy association with microbiological etiology

HIV-unexposed children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology did not differ in prevalence of thoracic lymphadenopathy compared to the absence thereof (10% vs 9%), (6% vs 6%) and (3% vs 4%), respectively.

HIV-unexposed children with culture confirmed PTB had a 3.9 fold (95% CI 1.1-13.9) higher odds of thoracic lymphadenopathy (6%) compared to the absence thereof (2%). Similarly HIV-unexposed children with culture or clinically confirmed PTB had a higher odds (aOR 2.8; 95% CI 1.4-5.5, 24% vs 11%) of thoracic lymphadenopathy, refer Table 9.5.

Likewise, HEU children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology did not differ in prevalence of thoracic lymphadenopathy compared to the absence thereof (0% vs 4%), (0% vs 4%) and (0% vs 3%), respectively. HEU children with culture or clinically confirmed PTB had a higher odds (aOR 2.6; 95% CI 1.1-5.9, 24% vs 11%) of thoracic lymphadenopathy compared to the absence thereof; refer Table 9.5.

HIV-infected children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology did not differ in prevalence of thoracic lymphadenopathy compared to the absence thereof (28% vs 21%), (11% vs 10%) and (0% vs 7%), respectively. Although not significant HIV-infected children with culture confirmed PTB and culture or clinically confirmed PTB trended towards thoracic lymphadenopathy (aOR 3.3; 95% CI 0.2-48.3, 6% vs 2%) and (aOR 2.0; 95% CI 0.6-6.2, 50% vs 40%), respectively; refer Table 9.5.

Table 9.5 Thoracic lymphadenopathy association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

	HIV-unexposed (N=428)				**HEU** (N=284)				**HIV-infected** (N=108)			
Microbiological etiology	**Thorax Lymph nodes** N=68 (%)	No Thorax Lymph nodes N=360 (%)	OR (95% CI)	aOR^ (95%CI)	**Thorax Lymph nodes** N=41 (%)	No Thorax N=243 (%)	OR (95%CI)	aOR^ (95% CI)	**Thorax Lymph nodes** N=18 (%)	No Thorax Lymph nodes N=90 (%)	OR (95% CI)	aOR^ (95% CI)
PQA* model probability index ≥ 0.5 for bacterial etiology	7 (10)	34 (9)	1.1 (0.4-2.7)	1.2 (0.5-2.9)	0 (0)	10 (4)	1.0	1.0	5 (28)	19 (21)	1.4 (0.5-4.5)	1.6 (0.5-5.4)
PQA* model probability index ≥ 0.6 for bacterial etiology	4 (6)	23 (6)	0.9 (0.3-2.7)	1.0 (0.3-3.0)	0 (0)	9 (4)	1.0	1.0	2 (11)	9 (10)	1.1 (0.2-5.7)	0.8 (0.2-4.7)
PQA* model probability index ≥ 0.7 for bacterial etiology	2 (3)	13 (4)	0.8 (0.2-3.7)	0.9 (0.2-4.2)	0 (0)	8 (3)	1.0	1.0	0 (0)	6 (7)	1.0	1.0
MCCP #	3 (4)	24 (7)	0.6 (0.2-2.2)	0.7 (0.2-2.5)	2 (5)	16 (6)	0.7 (0.2-3.2)	0.8 (0.2-3.4)	2 (11)	11 (12)	0.9 (0.2-4.4)	1.4 (0.2-8.0)
PQA* model probability index ≥ 0.5 for Respiratory Viral etiology	30 (44)	159 (44)	1.0 (0.6-1.7)	1.0 (0.6-1.7)	13 (32)	94 (39)	0.7 (0.4-1.5)	0.7 (0.3-1.4)	3 (17)	19 (21)	0.7 (0.2-2.9)	1.0 (0.2-4.0)
PQA model probability index ≥ 0.5 *Pneumocystis jiroveci* etiology	N/A	N/A	N/A	N/A	1 (2)	8 (4)	0.7 (0.1-6.0)	0.6 (0.1-5.3)	2 (11)	21 (23)	0.4 (0.1-1.9)	0.5 (0.1-2.7)
Culture Confirmed Pulmonary TB	4 (6)	8 (2)	2.8 (0.8-9.4)	**3.9(1.1-13.9)**	4/40 (10)	8/241 (3)	3.2 (0.9-11.3)	3.1(0.9-11.2)	1/17 (6)	2/85 (2)	2.6 (0.2-30.3)	**3.3(0.2-48.3)**
Culture or clinically confirmed pulmonary TB	16 (24)	38 (11)	2.6 (1.4-5.0)	**2.8(1.4-5.5)**	10 (24)	26 (11)	2.7 (1.2-6.1)	**2.6(1.1-5.9)**	9 (50)	36 (40)	1.5 (0.5-4.1)	**2.0(0.6-6.2)**

*PQA - PERCH Quantitative Analysis
Microbiologically Confirmed Pneumococcal Pneumonia
N/A: not applicable
^ adjusted for CXR-PEP, other infiltrate only, chronic lung disease and bilateral air trapping

9.2.6 Chest X-ray chronic lung disease association with microbiological etiology

HIV-unexposed children with a PQA model probability index for bacterial, respiratory viral etiology, culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of chronic lung disease compared to the absence thereof. Refer Table 9.6.

HEU children with a PQA model probability index for bacterial, respiratory viral etiology, and *Pneumocystis jiroveci* etiology did not differ in prevalence of chronic lung disease compared to the absence thereof. HEU children with culture confirmed PTB and culture or clinically confirmed PTB trended towards chronic lung disease (25% vs 4%; OR 8.1; 95% CI 0.8-83.9) and (25% vs 13%; OR 2.3; 95% CI 0.2-23.1), respectively. Refer Table 9.6.

HIV-infected children with a PQA model probability index $\geq$ 0.5 and $\geq$ 0.6 for bacterial etiology trended towards chronic lung disease (40% vs 21%; OR 2.5; 95% CI 0.4-15.6) and (20% vs 10%; OR 2.3; 95% CI 0.2-22.9). Similarly, HIV-infected children with culture or clinically confirmed PTB trended towards chronic lung disease (60% vs 41%; OR 2.2; 95% CI 0.3-13.6); refer Table 9.6.

Table 9.6 Chest X-Ray chronic lung disease association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

	HIV-unexposed (N=428)			**HEU** (N=284)			**HIV-infected** (N=108)		
Microbiological etiology	**Chronic Lung disease** N=5 (%)	No Chronic Lung Disease N=423 (%)	OR (95% CI)	**Chronic Lung disease** N=4 (%)	No Chronic Lung Disease N=280 (%)	OR (95% CI)	**Chronic Lung disease** N=5(%)	No Chronic Lung Disease N=103(%)	OR (95% CI)
PQA* model probability index ≥ 0.5 for bacterial etiology	0 (0)	41 (10)	1.0	0 (0)	10 (4)	1.0	2 (40)	22 (21)	2.5 (0.4-15.6)
PQA* model probability index ≥ 0.6 for bacterial etiology	0 (0)	27 (6)	1.0	0 (0)	9 (3)	1.0	1 (20)	10 (10)	2.3 (0.2-22.9)
PQA* model probability index ≥ 0.7 for bacterial etiology	0 (0)	15 (4)	1.0	0 (0)	8 (3)	1.0	0 (0)	6 (6)	1.0
MCCP [#]	0 (0)	27 (6)	1.0	0 (0)	18 (6)	1.0	0 (0)	13 (13)	1.0
PQA* model probability index ≥ 0.5 for Respiratory Viral etiology	4 (80)	185 (44)	5.1(0.6-46.4)	3 (75)	104 (37)	5.1 (0.5-49.4)	1 (20)	21 (20)	0.9 (0.1-9.2)
PQA model probability index ≥ 0.5 *Pneumocystis jiroveci* etiology	N/A	N/A	N/A	0 (0)	9 (3)	0.7 (0.1-5.9)	1 (20)	22 (21)	0.9 (0.1-8.7)
Culture Confirmed Pulmonary TB	0 (0)	12 (3)	1.0	1 (25)	11/277 (4)	**8.1 (0.8-83.9)**	0 (0)	3/97 (3)	1.0
Culture or clinically confirmed pulmonary TB	0 (0)	54 (13)	1.0	1 (25)	35 (13)	**2.3 (0.2-23.1)**	3 (60)	42 (41)	**2.2 (0.3-13.6)**

*PQA - PERCH Quantitative Analysis

[#] Microbiologically Confirmed Pneumococcal Pneumonia

N/A: not applicable

9.2.7 Bilateral Air Trapping association with microbiological etiology

HIV-unexposed children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology did not differ in prevalence of bilateral air trapping compared to the absence thereof (12% vs 9%), (7% vs 6%) and (2% vs 4%), respectively. Similarly HIV-unexposed children with culture confirmed PTB and culture or clinically diagnosed PTB did not differ in the prevalence of bilateral air trapping (3% vs 3%) and (13% vs 13%), respectively. Refer Table 9.7.

HEU children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology, ≥ 0.5 for respiratory viral etiology, ≥ 0.5 for *Pneumocystis jiroveci* etiology, MCCP, culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of bilateral air trapping compared to the absence thereof. Refer Table 9.7.

Similarly, HIV-infected children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology, ≥ 0.5 for respiratory viral etiology, ≥ 0.5 for *Pneumocystis jiroveci* etiology, MCCP, culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of bilateral air trapping compared to the absence thereof. Refer Table 9.7.

Table 9.7 Bilateral Air Trapping association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

	HIV-unexposed (N=428)			**HEU** (N=284)			**HIV-infected** (N=108)		
Microbiological etiology	**Bilateral air trapping** N=60 (%)	No Bilateral Air Trapping N=368 (%)	OR (95% CI)	**Bilateral air trapping** N=42 (%)	No Bilateral Air Trapping N=242 (%)	OR (95% CI)	**Bilateral air trapping** N= 21(%)	No Bilateral Air Trapping N=87 (%)	OR (95% CI)
PQA* model probability index ≥ 0.5 for bacterial etiology	7 (12)	34 (9)	1.3 (0.5-3.1)	0 (0)	10 (4)	1.0	4 (19)	20 (23)	0.8 (0.2-2.6)
PQA* model probability index ≥ 0.6 for bacterial etiology	4 (7)	23 (6)	1.1 (0.4-3.2)	0 (0)	9 (4)	1.0	3 (14)	8 (9)	1.7 (0.4-6.8)
PQA* model probability index ≥ 0.7 for bacterial etiology	1 (2)	14 (4)	0.4 (0.1-3.3)	0 (0)	8 (3)	1.0	1 (5)	5 (6)	0.8 (0.1-7.4)
MCCP [#]	2 (3)	25 (7)	0.5 (0.1-2.1)	2 (5)	16 (7)	0.7 (0.2-3.2)	0 (0)	13 (15)	1.0
PQA* model probability index ≥ 0.5 for Respiratory Viral etiology	22 (37)	167 (45)	0.7 (0.4-1.2)	20 (48)	87 (36)	1.6 (0.8-3.1)	4 (19)	18 (21)	0.9 (0.3-3.0)
PQA model probability index ≥ 0.5 *Pneumocystis jiroveci* etiology	N/A	N/A	N/A	1 (2)	8 (3)	0.7 (0.1-5.9)	5 (24)	18 (21)	1.2 (0.4-3.7)
Culture Confirmed Pulmonary TB	2 (3)	10 (3)	1.2 (0.3-5.8)	1/41 (2)	11/240 (5)	0.5 (0.1-4.1)	0 (0)	3/82 (4)	1.0
Culture or clinically confirmed pulmonary TB	8 (13)	46 (13)	1.1 (0.5-2.4)	4 (10)	32 (13)	0.7 (0.2-2.1)	8 (38)	37 (43)	0.8 (0.3-2.2)

[*] PQA - PERCH Quantitative Analysis
[#] Microbiologically Confirmed Pneumococcal Pneumonia
N/A: not applicable

9.2.8 Normal chest X-ray compared to any chest X-ray changes association with microbiological etiology

HIV-unexposed children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology, ≥ 0.5 for respiratory viral etiology, MCCP, culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of normal chest X-ray compared to the presence of any chest X-ray changes. Refer Table 9.8.

Similarly, HEU children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology, ≥ 0.5 for respiratory viral etiology, ≥ 0.5 for *Pneumocystis jiroveci* etiology, MCCP, culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of normal chest X-ray compared to the presence of any chest X-ray changes. Refer Table 9.8.

HIV-infected children with a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 for bacterial etiology trended towards a normal chest X-ray (43% vs 21%; OR 2.8; 95% CI 0.6-13.8), (29% vs 9%; 95% OR 4.1; 95% CI 0.7-24.2) and (14% vs 5%; OR 3.2; 95% CI 0.3-31.9), respectively compared to the presence of any chest X-ray changes. HIV-infected children with a PQA model probability ≥ 0.5 for respiratory viral etiology, ≥ 0.5 for *Pneumocystis jiroveci* etiology, MCCP, culture confirmed PTB and culture or clinically diagnosed PTB did not differ in prevalence of normal chest X-ray compared to the presence of any chest X-ray changes. Refer Table 9.8.

Table 9.8 Normal chest X-ray association with microbiological etiology based on the PERCH Quantitative Analysis (PQA) model predicted probability, microbiologically confirmed pneumococcal pneumonia, culture and culture or clinically confirmed pulmonary TB

	HIV-unexposed (N=428)			**HEU** (N=284)			**HIV-infected** (N=108)		
Microbiological etiology	**Normal chest X-ray** N=123 (%)	Any CXR Changes N= 305 (%)	OR (95% CI)	**Normal chest X-ray** N= 81(%)	Any CXR changes N=203 (%)	OR (95% CI)	**Normal chest X-ray** N=7 (%)	Any CXR changes N= 101(%)	OR (95% CI)
PQA* model probability index ≥ 0.5 for bacterial etiology	10 (8)	31 (10)	0.8 (0.4-1.6)	4 (5)	6 (3)	1.7 (0.5-6.2)	3 (43)	21 (21)	**2.8 (0.6-13.8)**
PQA* model probability index ≥ 0.6 for bacterial etiology	8 (7)	19 (6)	1.0 (0.4-2.5)	4 (5)	5 (2)	2.0 (0.5-7.8)	2 (29)	9 (9)	**4.1 (0.7-24.2)**
PQA* model probability index ≥ 0.7 for bacterial etiology	7 (6)	8 (3)	2.3 (0.8-6.3)	3 (4)	5 (3)	1.5 (0.4-6.5)	1 (14)	5 (5)	**3.2 (0.3-31.9)**
MCCP [#]	5 (4)	22 (7)	0.5 (0.2-1.5)	5 (6)	13 (6)	0.9 (0.3-2.8)	0 (0)	13 (13)	1.0
PQA* model probability index ≥ 0.5 for Respiratory Viral etiology	47 (38)	142 (47)	0.7 (0.4-1.2)	26 (32)	81 (40)	0.7 (0.4-1.2)	0 (0)	22 (22)	1.0
PQA model probability index ≥ 0.5 *Pneumocystis jiroveci* etiology	N/A	N/A	N/A	0 (0)	9 (4)	1.0	1 (14)	22 (22)	0.6 (0.1-5.2)
Culture Confirmed Pulmonary TB	2 (2)	10 (3)	0.5 (0.1-2.3)	2/79 (3)	10/202 (5)	0.5 (0.1-2.5)	0 (0)	3/95 (3)	1.0
Culture or clinically confirmed pulmonary TB	11 (9)	43 (14)	0.6 (0.3-1.2)	6 (7)	30 (15)	0.5 (0.2-1.2)	1 (14)	44 (44)	0.3 (0.1-2.3)

[*]PQA - PERCH Quantitative Analysis

[#] Microbiologically Confirmed Pneumococcal Pneumonia

N/A: not applicable

9.3 Discussion: Objective 4

In the era post national immunization for HibCV and PCV vaccines in South African children, HIV-unexposed children with a PQA model probability index ≥ 0.5 for bacterial etiology had 2-fold greater odds for CXR-PEP compared to non CXR-PEP. Similarly HIV-unexposed children with MCPP had 3-fold greater odds of CXR-PEP compared to non CXR-PEP cases. These findings support the previous studies by Korppi *et al* and Virkki *et al* that air space/alveolar consolidation is predominantly associated with bacterial infection (65, 69). This also supports the findings by Vuori-Holopainen *et al* who investigated microbiology and chest X-ray patterns using lung aspiration and polymerase chain reaction (PCR) who found that 80% of the air space/alveolar consolidation was due *S. pneumoniae,* 10% due to atypical bacteria and 5% due to respiratory viral infection (96).

The WHO-defined standardized definition of CXR-PEP (15), was developed for HiB and PCV vaccine efficacy trails, and our findings support the findings of previous vaccine efficacy trials in children that demonstrated an association between CXR-PEP and *S. pneumoniae* and Hib pneumonia (17, 18, 159, 160). This supports that the literature that CXR-PEP may be an important proxy for these bacterial pathogens in pneumonia epidemiological studies in children.

Conversely, in HIV-unexposed children CXR-PEP was predominantly due to respiratory viral etiology i.e.: 15% of HIV-unexposed children with a PQA model probability index ≥ 0.5 for bacterial etiology had CXR-PEP, while 50% of children with a PQA model probability index ≥ 0.5 for respiratory viral etiology had CXR-PEP. These findings supports literature which demonstrated no association between chest X-ray pattern and putative microbiological etiology (63, 64, 68, 94, 95). The heterogeneity of microbiological methods used for

diagnosing bacterial pneumonia (63, 64, 68, 69, 94), with no available gold standard for diagnosing bacterial pneumonia (98), and limited number of microbes investigated in studies (63, 64, 68, 69), makes direct comparisons of our study findings to the literature difficult. Furthermore, the lack of standardized reporting on the definition of "chest X-ray pneumonia" in the different studies, significant variability in the application of WHO standardized chest X-ray reporting (71, 73, 77-81) and the reporting of chest X-rays by a single radiologist in certain studies (62, 68, 94) is important when making direct comparisons of our study findings to the literature. The different epidemiological settings, limited cohort size in certain studies (63, 68, 69, 94), inclusion of both ambulatory and hospitalized children in certain studies, timing of the chest X-ray on hospitalization (63, 64) also needs to be considered.

In all 3 groups i.e.: HIV-unexposed, HEU and HIV infected, the sensitivity of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for bacterial etiology was low, and similarly the sensitivity of CXR-PEP in predicting MCPP was low, with a low positive predictive value, but higher specificity and a high negative predictive value. This supports the literature from previous Hib and PCV clinical trials that this CXR-PEP finding is more specific, rather than sensitive for demonstrating vaccine efficacy (17, 161, 162), using WHO-defined standardized chest X-ray interpretation methods (15). Our study findings supports previous literature that WHO-defined CXR-PEP may have under-estimated the burden of pneumonia prevented by HibCV and PCV vaccination, especially in a high HIV prevalence setting (16, 123). This may support the proposal by Madhi *et al* that the inclusion of other infiltrate with a raised CRP $\geq$40 mg/dL as an end-point when evaluating PCV efficacy, which may assist in capturing bacterial pneumonia cases without evidence of CXR-PEP (122).

HIV-infected children with a PQA model probability index $\geq$ 0.5 for respiratory viral etiology and a PQA model probability index $\geq$ 0.5 for *Pneumocystis jiroveci* etiology trended

towards CXR-PEP. The limitation in this study was the small number of HIV-infected children (n=108) enrolled, hence we had limited power. The sensitivities of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for respiratory viral etiology and CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for *Pneumocystis jiroveci* etiology was high, but had low positive predictive values, lower specificities and a high negative predictive values. These findings support the findings by Madhi *et al* in the same study population in Soweto between 1997 and 1998, before the national immunization program for PCV, who found that respiratory viral infection was more likely to present with alveolar consolidation in HIV-infected compared to HIV-uninfected (p=0.02) (62). Our findings also supports the results of previous vaccine efficacy studies and reviews by Madhi and Klugman *et al*, in South Africa pre PCV and post PCV, that the high prevalence of CXR-PEP in HIV-infected children due to opportunistic infections like *Pneumocystis jiroveci* pneumonia and respiratory viral infections may limit the use of CXR-PEP as an outcome measure for vaccine efficacy and impact studies in HIV-infected children (62, 122, 163).

In HIV-infected children using the PQA model probability index $\geq$ 0.5 for *Pneumocystis jiroveci* etiology; the most common finding was CXR-PEP (26%), followed by bilateral air trapping (24%). This is lower than that described in a recent review article of 7 studies, with 11 children diagnosed with *Pneumocystis jiroveci* pneumonia where the most common finding was "homogenous opacification" prevalent in 45% of children (109). The different study setting and the timing of the hospital presentation of these children could possibly account for the differences in our findings compared to this review article.

HIV-infected children with a PQA model probability index $\geq$ 0.5, $\geq$0.6 and $\geq$ 0.7 for bacterial etiology trended towards a normal chest X-ray compared to any chest X-ray changes. As described in chapter 7 of this thesis, 82% of HIV-infected children had severe immune suppression, while only 29% were on anti-retroviral therapy prior to being hospitalized for

WHO-defined severe or very severe pneumonia. This supports the findings by Du Plessis *et al* who found that HIV-infected children with immune suppression were 50% less likely to have air space disease (115). This may be due to decreased ability to mount an immune response in the presence of infection and manifest chest X-ray changes in severely immune suppressed HIV-infected children as described in the literature (117), as majority of the HIV-infected children had severe immune suppression in our study.

Furthermore Nortan *et al* found that HIV-infected children with significantly lower mean CD4 counts and higher viral loads had an increased incidence of chronic chest X-ray changes. However on follow up, these chest X-ray changes resolved over time in many children with significantly lower CD4 counts and without associated clinical improvement, supporting the finding of decreased clinical ability to mount an immune response in severely immune suppressed HIV-infected children (117).

In HIV-unexposed children with culture or clinically confirmed PTB 14% had CXR-PEP, while 24% had thoracic lymphadenopathy, which was the most common finding. This supports the findings by Milkovic *et al* investigating the chest X-ray findings in 172 children with primary TB who also found that lymphadenopathy (84%) was the most common finding (111). However we found a much lower prevalence of thoracic lymphadenopathy compared to this study, but our findings were similar to Srinakarin *et al* who found thoracic lymphadenopathy in 33% of HIV-uninfected children with PTB (114). Although thoracic lymphadenopathy is the "radiological hallmark" of pulmonary TB on chest X-ray (105, 107, 108, 164), a significant limitation is the poor inter-reader agreement reported in the literature (99, 102, 110, 165, 166), which could also account for the different prevalence of lymphadenopathy.

In all 3 HIV exposure groups the sensitivity of CXR-PEP in predicting culture and culture or clinically confirmed PTB was low, with a very low positive predictive value, better specificity and high negative predictive values. Our findings that CXR-PEP is not sensitive for diagnosing PTB is supported by the current literature (99, 109). HIV-unexposed children with culture confirmed PTB were 4-fold more likely to have thoracic lymphadenopathy compared to the absence thereof, while HIV-unexposed and HEU children were 3-fold more likely to have thoracic lymphadenopathy. To our knowledge this is the first study to describe the chest X-ray findings in HEU children with culture confirmed and culture or clinically confirmed PTB. Although not significant HIV-infected children with culture confirmed PTB and culture or clinically confirmed PTB trended towards thoracic lymphadenopathy. Our findings that thoracic lymphadenopathy is the most common finding (24-50%), and the "radiographic hallmark" in children with culture confirmed or clinically diagnosed PTB, regardless of HIV-exposure status, is supported by the literature (105, 107, 108, 111, 112).

In the literature, miliary infiltrate is an important finding in PTB in HIV-uninfected children with PTB (102, 167, 168). We did not demonstrate an association between HIV-unexposed children with culture or culture or clinically confirmed PTB and miliary infiltrate. However in chapter 7 of this thesis we described that HIV-infected children had a 2-fold greater odds of miliary infiltrate compared to HIV-unexposed children. In this chapter we found that HIV-infected children culture confirmed PTB had a 14-fold higher likelihood of miliary infiltrate on chest X-ray and culture or clinically confirmed PTB had a 4-fold higher likelihood of miliary infiltrate on chest X-ray. Hence miliary infiltrate may be an important chest X-ray feature in HIV-infected children with culture confirmed PTB and culture or clinically confirmed PTB.

9.4 Limitations: Objective 4

A limitation of this study is the small number of HIV-infected children (n=108) enrolled. Thus we may have had limited power when evaluating for the association between chest X-ray patterns and microbiological etiology in HIV-infected children, although trends were demonstrated in our study.

A further limitation is that chronic lung disease had a very low prevalence in our study: HIV-unexposed (5%), HEU (1%) and HIV-infected (1%) as described in chapter 5 of this PhD thesis. Hence we had limited power to evaluate for the association between chronic lung disease and microbiological etiology in this study, although trends were also demonstrated.

The PQA model, a partially latent class model developed in the PERCH study was used (148, 149), details of which are described in the methods chapter 3 of this PhD thesis. Briefly the PQA model takes into consideration the sensitivity and specificity of the tests used to identify respiratory pathogens in PERCH cases and controls using silver standard (e.g., lung aspirate) and bronze standard (e.g., NPOP and IS) data (148, 149). The limitation of our study was that the number of cases that had silver standard (lung aspiration) was low (ie: 6 children). Hence the PQA model was biased towards bronze standard data. However as described in the literature to date there is no clinically acceptable "gold standard" for the microbiological diagnosis of bacterial pneumonia that has both high sensitivity and specificity, is minimally invasive and readily available (98).

The PQA model "assumes there are no interactions between pathogens (i.e. conditional independence) and does not allow for synergistic co-infections with multiple pathogens. For each case a probability distribution of each of the 33 pathogens is estimated, generating an

etiologic histogram" (148, 149). The role of poly-microbial infections in the pathogenesis of childhood pneumonia, especially in HIV-infected children is well described (32). Therefore the limitation of the PQA model, may be biased towards specific pathogens when co-infection may have existed.

The MCCP yield in this study was low (7%) of children. This is in keeping with previous literature that blood culture has low sensitivity (2-3%) for bacterial diagnosis in children hospitalized with CAP (62, 95). There was a low prevalence (4-11%) for bacterial etiology based on a PQA model probability index ≥ 0.5, ≥ 0.6 and ≥ 0.7 in HIV-unexposed children. Hence we had limited power to evaluate for the association between chest X-ray patterns and bacterial etiology.

For the TB analysis we performed 2 separate analyses: culture confirmed PTB and culture or clinically confirmed PTB. This is supported by the current literature that diagnosis of PTB is difficult in children due to non-specific clinical signs and limited utility of the tuberculin skin test, especially in HIV-infected children (37, 99). Sputum smear microscopy from gastric washings and induced sputa have a low yield (4% to 7%) (100), with TB culture producing better, but low yields of approximately 7% to 30%, but takes longer time for results (101-104).

Due to the difficulty in obtaining microbiological confirmation of PTB in children, diagnosis often relies on a combination of clinical features, chest X-ray findings and microbiology (102, 105). Hence our analysis of culture or clinically confirmed PTB may be biased as clinicians would have used the chest X-ray to make the clinical diagnosis of PTB. However our methodology is similar to that described by Pitcher *et al* where a diagnosis of PTB was made in 14% of children using both clinical or culture confirmed PTB 3/37 (24%) culture-confirmed PTB and 34/37 (92%) clinically diagnosed PTB (104).

9.5 Future Research on Chest X-ray Findings and Microbiological Etiology

As described in the literature to date there is no clinically acceptable "gold standard" for the microbiological diagnosis of bacterial pneumonia that has both high sensitivity and specificity, is minimally invasive and readily available (98). Future research on the association of chest X-ray findings and microbiological bacterial etiology would involve a combination of lung aspiration in areas of CXR-PEP, in a larger sample size of children hospitalized WHO defined severe and very pneumonia, using radiological techniques like ultrasound guidance and microbiological testing for etiology using novel molecular diagnostics like multiplex polymerase chain reaction. In chapter 8 of this thesis we demonstrated that CXR-PEP were 2.5 fold (95% CI 1.5-4.0) more likely to be associated with the composite outcome of mechanical ventilation or death, in children with WHO defined severe or very severe pneumonia. Hence a combination of post-mortem studies using novel molecular diagnostics to determine microbiological etiology and radiological investigations like post-mortem chest X-ray, ultrasound and CT chest would also be very important.

As described in the limitations of this chapter, the PQA model "assumes there are no interactions between pathogens (i.e. conditional independence) and does not allow for synergistic co-infections with multiple pathogens, example bacterial and respiratory viral co-infection. Multiple microbiological pathogens identification remains a "methodological and analytical challenge." Future research would involve investigating the role of microbiological synergistic co-infections and chest X-ray patterns.

10 Objective 5: Chest X-ray Patterns and Computer Aided Diagnosis: Methods, Results, Discussion, Limitations

Objective: To determine the sensitivity and specificity of computer aided diagnosis (CAD4WHOKids) for CXR-PEP versus non CXR-PEP compared to a consensus human interpretation used a reference standard.

10.1 Methods

10.1.1 International Collaboration

This study was an international collaboration between Dr N. Mahomed from the University of Witwatersrand Johannesburg, South Africa and the Diagnostic Image Analysis Group, Professor B van Ginneken, R Philipsen and J Melendez from Radboud UMC, Nijmegen, The Netherlands.

Prof Van Ginneken is one of the leading international researchers on computer aided diagnosis on chest X-rays in adults with pulmonary TB, with development of the CAD4TB software. This is the first opportunity for the Diagnostic Image Analysis Group to work on CAD in chest X-rays in children under 5 years, through this international collaboration with a paediatric trained radiologist, Dr N Mahomed. Through this international collaboration the software CAD4WHOkids was developed.

Dr N Mahomed and Professor SA Madhi are both on the WHO CRES committee. Dr N Mahomed conceptualized this study and approached Professor Van Ginneken with her proposal on the development of CAD for WHO standardized chest X-ray interpretation in children less than 5 years. Communication was through tele-conferencing and Professor Van Ginneken and Mr Rick Philipsen personally visited the University of Witwatersrand, South Africa in November 2015 to collaborate on this study.

10.1.2 Study Setting- PERCH Study, South Africa

This study was nested within the PERCH study, South African site based at Chris Hani Baragwanath Academic Hospital, Johannesburg. The full details of this study were described in the methods chapter of this thesis. Briefly, enrolment at the South African PERCH site was over a 2 year period, during which 920 children with WHO-defined severe or very severe pneumonia were enrolled in South Africa and chest X-rays were available in 885 (96%) cases.

10.1.3 Summary of Chest X-ray Findings

The full details of the chest X-ray findings in this study are described in objective 2 of this PhD thesis, chapter 7. WHO standardized chest X-ray conclusions were used (15). Briefly using the majority consensus reading of 858 interpretable chest X-rays, 333 (39%) had CXR-PEP, 208 (24%) had other infiltrate only (without CXR-PEP) and 317 (37%) had no CXR-PEP or other infiltrate only.

10.1.4 Computer Aided Diagnosis (CAD4WHOKids) of Chest X-Rays in Children

10.1.4.1 Data set manual marking

The entire data set of South African PERCH chest X-rays were stored in a digital format, Joint Photographic Experts Group (JPEG), with 256 grey levels (8 bit). The 858 interpretable chest X-rays were analysed in this study. Using the majority consensus reading the principle investigator, Dr N Mahomed used the program Paint.Net to manually outline the areas of CXR-PEP in the 333 chest X-rays, and the areas of other infiltrate only in 208 chest X-rays.

10.1.4.2 Automatic Lung Segmentation

The first step of the computer analysis involved automatic lung field segmentation, as the structures of interest are the lung fields. From the 858 interpretable chest X-rays, the lung fields were manually outlined in 25% (214/858) randomly selected chest X-rays. This was used to train the CAD4WHOKids software to segment the lung fields and automatically segment the

lung fields of the remaining chest X-rays following the approach described by Van Ginneken *et a*l (169). This approach computes a set of filtered versions of the image from convolutions with the two-dimensional Gaussian function and its derivatives up to second order, at 5 scales. The output of these filters at each pixel is used as a feature vector for that pixel, augmented with the spatial coordinates of that pixel as two additional features. These features vectors are used to train a k-nearest neighbour classifier to classify each pixel as belonging to the object i.e.; right lung, left lung or background. Once the classifier has been trained on the 214 chest X-rays, this was applied to each image and provided a probability for each pixel as belonging to right lung, left lung or background. These lung probability maps were smoothed and post-processed with mathematical morphology filters (169).

The automated lung segmentations were manually inspected and if deemed inadequate, they were adjusted manually. From the chest X-rays which had automated lung segmentation (n=644), manual inspection demonstrated 237 (37%) of chest X-rays to have inadequate automatic lung field segmentation, hence these chest X-rays were manually adjusted. The required adjustments were minor involving the superior mediastinum in most cases. The motivation for manually correcting the outlines was to analyse the performance of CAD4WHOKids software texture analysis, undisturbed by errors in the lung field extraction.

Compared to adults there are greater technical challenges with regards to automatic lung field segmentation on chest X-ray in children as the mediastinum and cardio-thoracic ratios have different ranges in children under 5 years. Variability in the thymic size in children accounts for variability in the superior mediastinum size in children in this age group (25, 170, 171).

10.1.4.3 Texture Analysis

In CAD4WHOKids, texture analysis is used to assign a probability to each location in the lung fields for it to belong to a region of CXR-PEP. This is comparable to the approach taken by Van Ginneken *et a*l using the software CAD4TB, where a similar analysis is performed to determine if locations in the lung fields are similar to abnormal regions outlined in chest X-rays of adults investigated for TB, as described in the literature (172). First, all images were rescaled to a width of 1024 pixels. The pixels from outlined regions of CXR-PEP and other infiltrates were used as examples of abnormal pixels, and pixels in the lung fields from images without outlines (no CXR-PEP or other infiltrate only) were used as examples of normal pixels. In order to train a classifier to produce a probability that a pixel belongs to the abnormal class, each pixel needs to be described by a feature vector. This vector of numbers should capture the image information at that location. To obtain this vector, pixel data was filtered with Gaussian derivatives through second order (zero order, first order derivatives to *x* and *y*, second order derivatives to *xx*, *xy*, and *yy*) on scales of 1, 2, 4, and 8 pixels. For every 8^{th} pixel in vertical and horizontal direction, the first four moments (mean, standard deviation, skew, kurtosis) in a local circular neighbourhood with radius 32 pixels were computed for every filtered image plus the original image as a set of texture features. With 25 filtered images and 4 moments, this results in 100 features. Additionally, several spatial context features for each pixel were also calculated: the *x*- and *y*-coordinates (normalized to the height of the image), the *x*- and *y*-coordinates in the bounding box of the lungs, and the distance to the lung wall.

This feature set can be used to classify every 8^{th} pixel and values in between are interpolated. Classification was done with a Support Vector Machine with radial basis kernel, using the implementation from LIBSVM. This classifier has two hyper parameters, the width of the radial basis function and the penalty term C, that are estimated from the data during training. The same

system was used as in CAD4TB: filters, every 8th pixel in a 32 pixel radius, 4 moments of filter responses and position features (172).

Training was done in 10-fold cross validation. This means the data is divided in 10 groups, and every group is classified with a system trained on the other 90% of images. Importantly the training chest X-rays were not used for the test chest X-rays. To visualise the working of the texture system, for each image a colour heat map was generated with red representing high likelihood of being abnormal, yellow intermediate, green low, and blue very low.

10.1.4.4 Image Score using a Quantile Rule

The proposed texture analysis system provides a likelihood of a textural abnormality being present for each pixel in the lung fields. In order to classify an image, these pixel scores were summarized into a single score. To compute a single score for each image, all pixel scores were sorted and the 95% percentile of all scores was determined using the SVM classifier system. This simple summary statistic has been shown to provide good performance in previous work by the Diagnostic Image Analysis Group (173).

10.1.4.5 Computer Aided Diagnosis vs Independent Human Reading

A consensus of 3 readers was used as the reference standard. In order to put the performance of the computer system in perspective, it is common practice to compare it with an external independent human reading. This reading was done by the principle investigator. Blinded to the reference consensus reading, the principle investigator scored a set of 200 randomly selected chest X-rays from the 858 data set (ie: stratified randomization 100 randomly selected chest X-rays with CXR-PEP and 100 randomly selected chest X-rays with no CXR-PEP or other infiltrate only. The principle investigator scored each image between 0 and 100, where 0 indicates certainty that the image is normal and 100 indicates certainty that the image is

abnormal. By varying the thresholds on these scores, a receiver operating characteristic curve (ROC) was created for the human reader, as well as, for the computer software.

10.1.4.6 Computer Aided Diagnosis on Chest X-ray, Analysis by HIV exposure status

Analysis using CAD4WHOKids for CXR-PEP vs non CXR-PEP was also done by HIV-exposure status i.e.: HIV-unexposed, HEU and HIV-infected children. CXR-PEP was prevalent in 163/428 (38%) of HIV-unexposed, 94/284 (33%) of HEU and 65/108 (60%) of HIV-infected children as described in the results of objective 2, chapter 7 of this PhD thesis.

10.1.5 Data Analysis

Data was analysed using STATA software, version 13.0 (StataCorp, College Station, Texas). To compare the results of CAD4WHOKids to the WHO standardized chest X-ray 3 reader consensus reading as the reference standard, two-two-tables was generated using Chi-squared test or Fisher's exact test as appropriate. From these, sensitivity, specificity, positive predictive value and negative predictive values and areas under the ROC curve were generated. Statistical significance was set as a two-tailed *P*-value of <0.05. The area under the ROC curve was utilized as a performance measure of the software CAD4WHOKids.

10.1.6 Budget

Funding for this study was from the Carnegie PhD fellowship fund (Grant no: B8749.R01) awarded to the principle investigator of this study Dr Mahomed. Funding was primarily for the developmental costs for the software CAD4WHOkids in collaboration with the Diagnostic Image Analysis Group, Radboud UMC, The Netherlands.

10.2 Results

10.2.1 Computer Aided Diagnosis for CXR-PEP vs non CXR-PEP Compared to Consensus Radiologist Reading Reference Standard

For CXR-PEP versus non CXR-PEP, using the 858 interpretable chest X-rays, where 333 chest X-rays had CXR-PEP, CAD4WHOKids had a sensitivity of 76%, specificity of 80% and area under the ROC curve of 0.850 (95% CI 0.823-0.876) compared to the radiologist consensus reading used as the reference standard. Refer Figure 10.1.

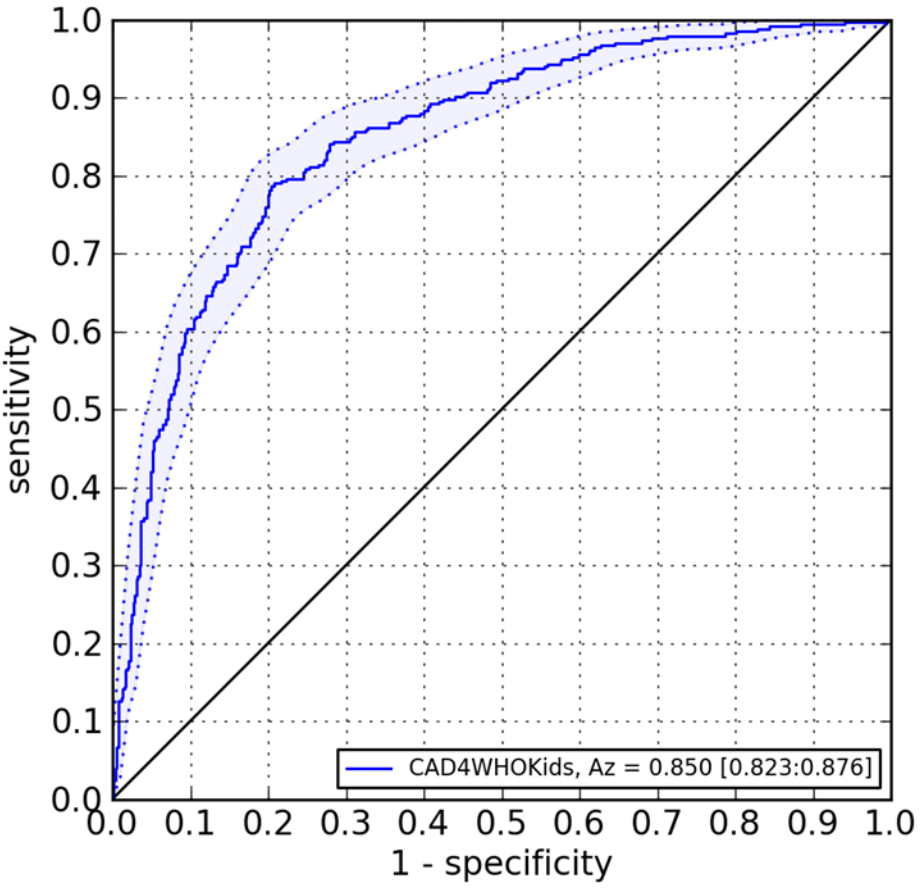

Figure 10.1: ROC curve (with 95 % CI) for CXR-PEP vs non CXR-PEP from the 858 chest X-rays CAD4WHOKids had a sensitivity of 76%, specificity of 80% and area under the ROC curve of 0.850 (95% CI 0.823-0.876) using the radiologist consensus reading as the reference standard.

10.2.2 Computer Aided Diagnosis for CXR-PEP vs Other Infiltrate Only Compared to Consensus Radiologist Reading Reference Standard

For WHO CXR-PEP versus other infiltrate only; where normal chest X-rays were excluded, from the 541 chest X-rays, where 333 had CXR-PEP and 208 had other infiltrate only, CAD4WHOKids had a sensitivity of 77%, specificity of 73%, and area under the ROC curve of 0.810 (95% CI 0.772-0.846). Refer Figure 10.2.

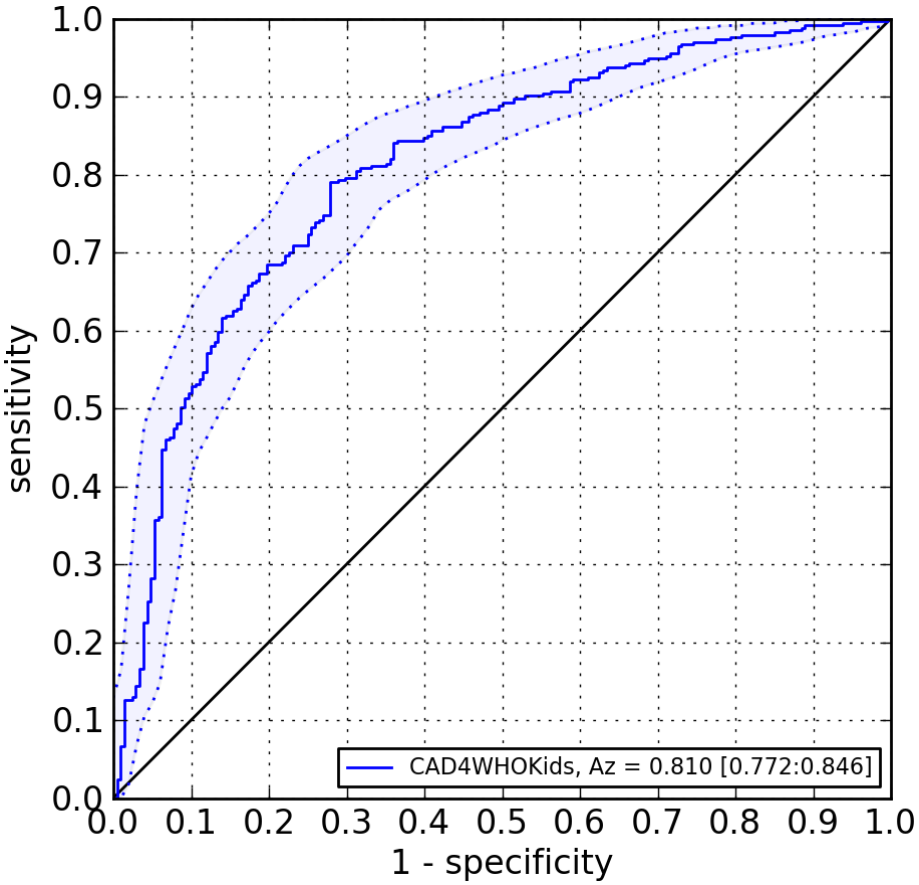

Figure 10.2: ROC curve (with 95% CI) for CXR-PEP vs other infiltrate only, from 541 chest X-rays CAD4WHOKids had a sensitivity of 77%, specificity of 73%, and area under the ROC curve of 0.810 (95% CI 0.772-0.846) using the radiologist consensus reading as the reference standard.

10.2.3 Colour Heat Map on Chest X-ray

To visualise the working of the texture system, for each image a colour heat map was generated with red representing high likelihood of being abnormal texture, yellow intermediate, green low, and blue very low. The test chest X-rays with areas of CXR-PEP and corresponding colour heat maps results are demonstrated in Figure 10.3.

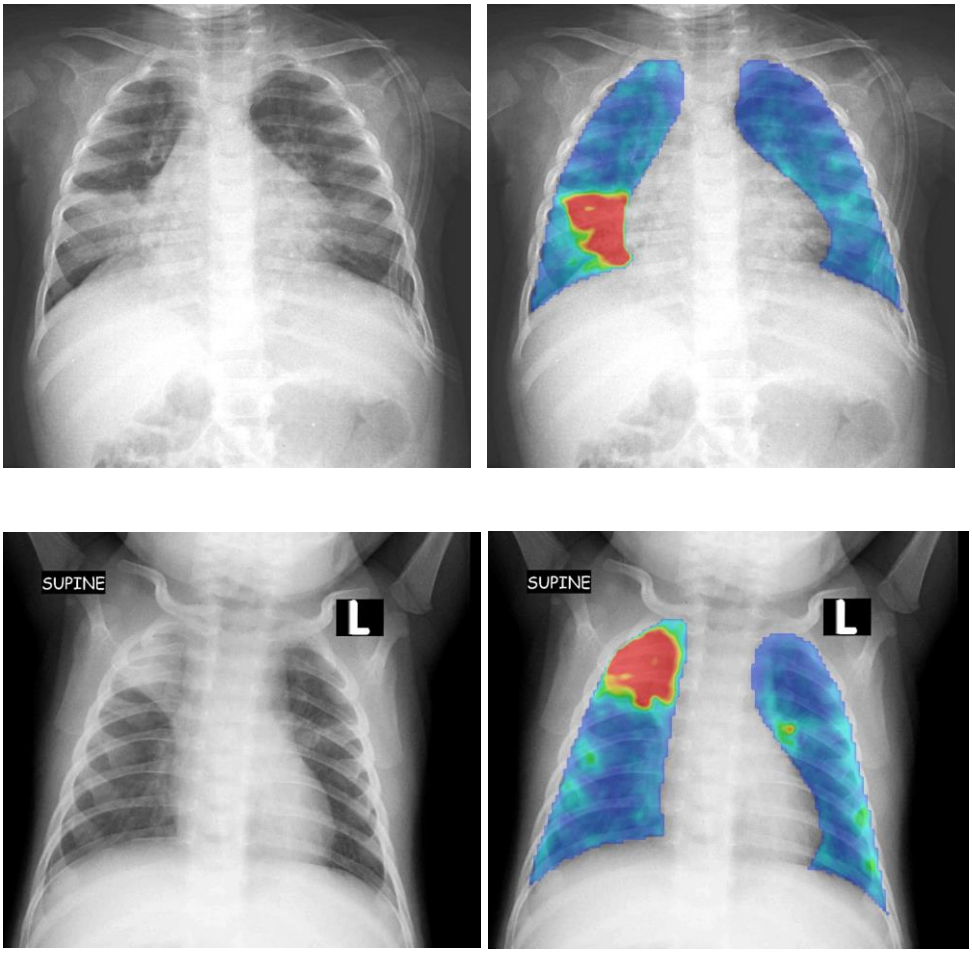

Figure 10.3: Colour heat map: to visualise the working of the texture system, for each chest X-ray a colour heat map was generated with red representing high likelihood of being abnormal, yellow intermediate, green low, and blue very low. The 2 examples represented here demonstrate good correlation between the areas of CXR-PEP and the results of the software CAD4WHOKids colour heat map and on the test chest X-rays.

10.2.4 Computer Aided Diagnosis vs Independent Human Reading

Using the independent scoring system for CXR-PEP versus non CXR-PEP, from the 200 randomly selected chest X-rays, the principle investigator had a sensitivity of 94%, specificity of 90% and area under the ROC curve of 0.975 (95% CI 0.955-0.991) using the radiologist consensus reading as the reference standard. This was better than the computer software CAD4WHOKids. This is shown in Figure 10.4.

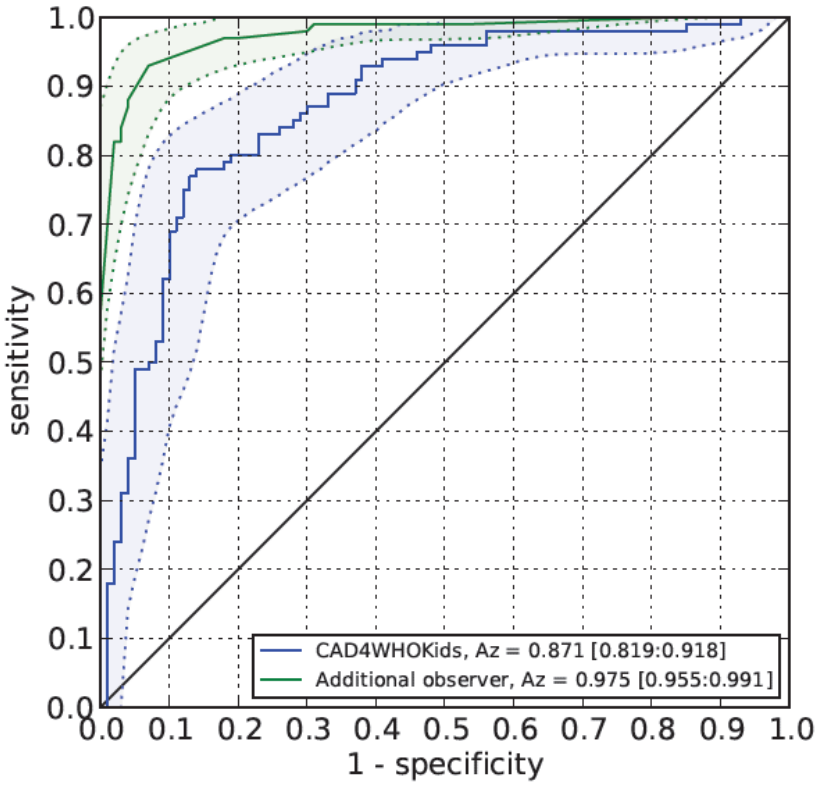

Figure 10.4: ROC curve with 95% CI from 200 randomly selected chest X-rays, comparing independent scoring system by the principle investigator (additional observer) for CXR-PEP versus non CXR-PEP and the CAD4WHOKids system.

10.2.5 Computer Aided Diagnosis on Chest X-ray, Analysis by HIV exposure status

Analysis using CAD4WHOKids for CXR-PEP vs non CXR-PEP was also done by HIV-exposure status. The area under ROC curve for CAD4WHOKids was 0.845 (95% CI 0.806-0.881) in HIV-unexposed children (n=428; refer Figure 10.5), 0.850 (95% CI 0.801-0.895) among HEU children (n=284; refer Figure 10.6) and 0.814 (95% CI 0.726-0.892) for HIV-infected children (n=108; refer Figure 10.7).

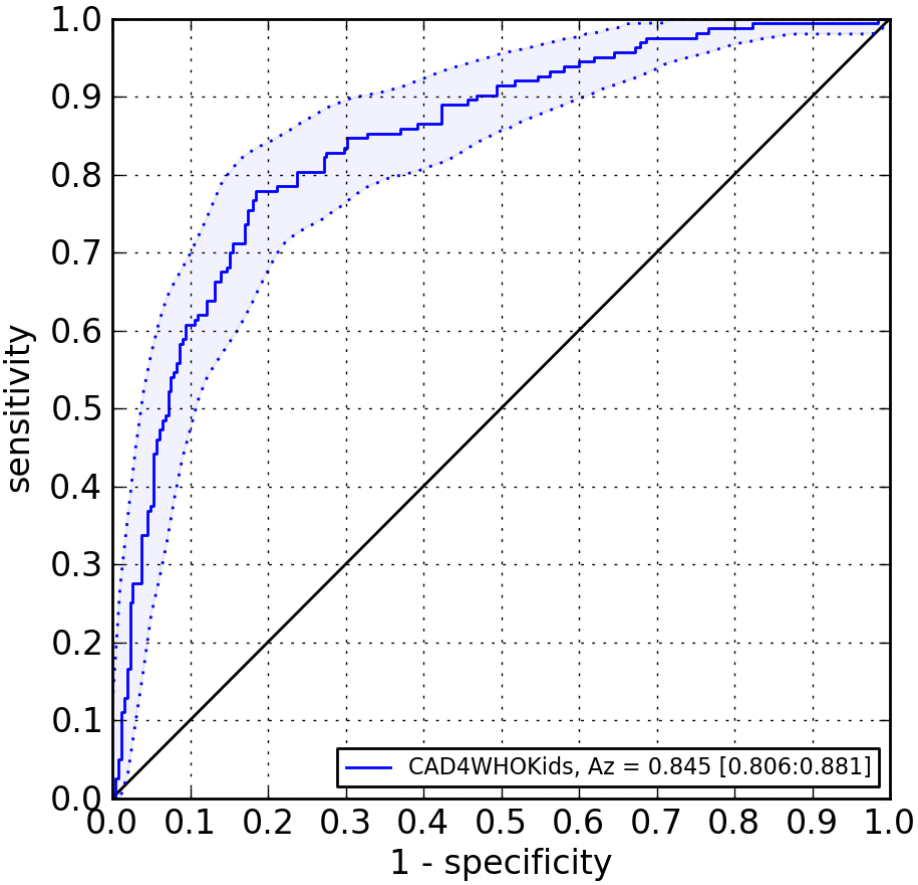

Figure 10.5: ROC curve (with 95% CI) for CXR-PEP vs non CXR-PEP in 428 HIV-unexposed children. CAD4WHOKids had a sensitivity of 80%, specificity of 76% and area under the ROC curve of 0.845 (95% CI 0.806 – 0.881) using the radiologist consensus reading as the reference standard.

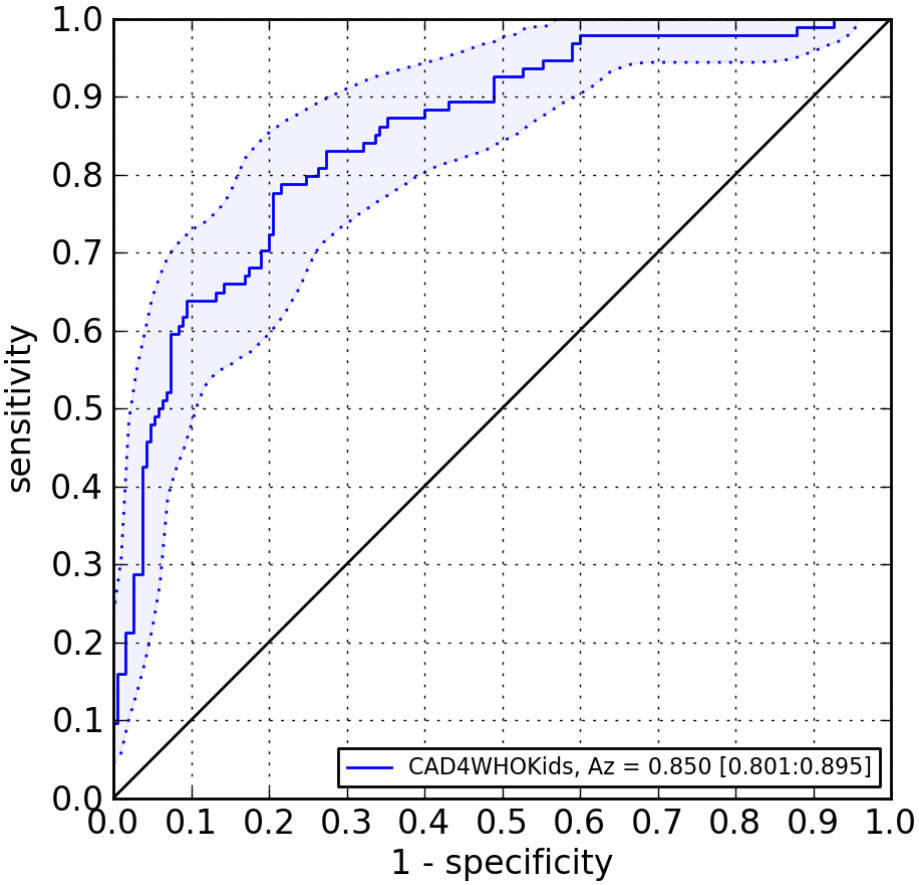

Figure 10.6: ROC curve (with 95% CI) for CXR-PEP vs non CXR-PEP in 284 HEU children. CAD4WHOKids had a sensitivity of 80%, specificity of 75% and area under the ROC curve of 0.850 (95% CI 0.801-0.895) using the radiologist consensus reading as the reference standard.

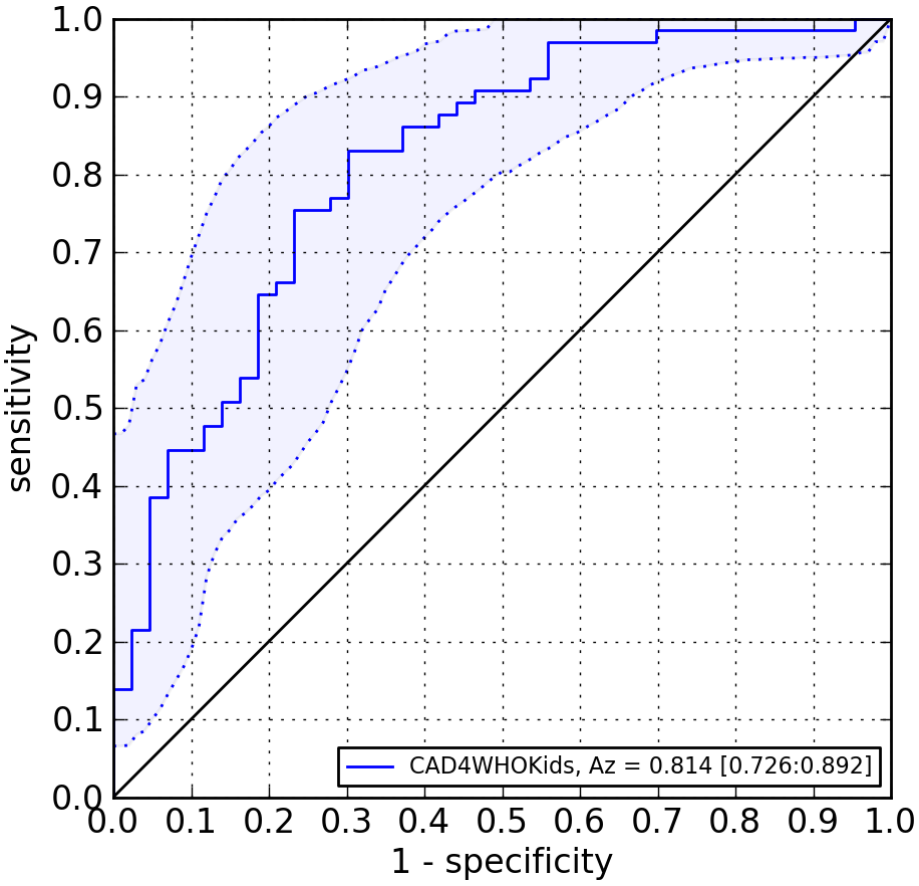

Figure 10.7: ROC curve (with 95% CI) for CXR-PEP vs non CXR-PEP in 108 HIV-infected children. CAD4WHOKids had a sensitivity of 75%, specificity of 77% and area under the ROC curve of 0.814 (95% CI 0.726-0.892) using the radiologist consensus reading as the reference standard.

10.3 Discussion: Objective 5

In this study we demonstrated that CAD4WHOKids software using textural analysis generated an area under the ROC curve of 0.850 for identifying CXR-PEP compared to non CXR-PEP, in which the radiologist consensus reading was used as the reference standard. The high sensitivity and specificity for CXR-PEP by CAD4WHOKids, as evident by the ROC curve of 0.810, was

maintained when limiting analysis to those CXRs arbitrated by the radiologist panel as having at least CXR-PEP or other infiltrate, i.e. excluding cases without CXR-PEP and other infiltrate only. Using WHO standardized chest X-ray interpretation criteria, CXR-PEP is a measure against which the efficacy of PCV impact studies and pneumonia epidemiological studies are performed (15). CAD4WHOKids textural analysis results are promising in identifying CXR-PEP and may have an important role especially in settings where there is limited clinical expertise in the interpretation of paediatric chest X-rays using WHO standardized methodology.

Mouton *et al* used CAD textural analysis to identify PTB, which has a different radiographic pattern. Our results are comparable to this study on CAD on chest X-rays in children who found an area under the ROC curve of 0.782 (0.655 -0.937) (127). Unlike Mouton *et al* we did not find significant errors using CAD4WHOKids classifier, in the peri-hilar or basal areas of the lung fields or left lung fields (127).

Oliveira *et al* found that the software Pneumo-CAD using the Haar wavelet textural analysis, had sensitivity of 100%, specificity of 80% and area under the ROC curve of 0.97. However, this study was limited by a very small sample size of 60 children, and poor chest X-ray quality as chest X-rays were photographed from a light box using a digital camera with low resolution and bit depth, which is not advised by the WHO standardized chest X-ray interpretation guidelines (15, 132).

A strength of our study was the large sample size of 858 children, compared to other studies, where the number of features used for classification or feature selection on CAD chest X-rays exceeded the number of chest X-ray with abnormalities. Furthermore, we showed that HIV-exposure and infection status did not materially affect the CAD interpretation of chest X-rays,

with the ROC curve ranging from 0.814 to 0.850, even though the percentage of CXR-PEP in each of the HIV-groups varied from 33% to 60%. Refer chapter 5 of PhD thesis for these detailed chest X-ray findings.

Using an independent human reading with use of the independent scoring system for CXR-PEP versus non CXR-PEP, the sensitivity, specificity and area under the ROC curve is comparable to the consensus 3 reader interpretation, which was used as the reference standard on this database.

The literature demonstrates that using WHO standardized chest X-ray interpretation definitions (15), chest X-ray human readers achieved moderate to substantial agreement (*Kappa*=0.48-0.62) for WHO end-point consolidation and lower agreement; i.e.: fair to moderate agreement (*Kappa*=0.27-0.66) for other infiltrate (119-121). CAD4WHOKids software textural analysis generated an area under the ROC curve of 0.850 for identifying CXR-PEP compared to non CXR-PEP, and an area under the ROC curve of 0.810 for identifying CXR-PEP compared to other infiltrate only. This software performed better than the described inter observer agreement by human interpretation as described in the literature using standardized chest X-ray definitions (119-121).

10.4 Limitations: Objective 5

Limitations of this study included that JPEG format chest X-rays were used, which is not optimal because there is some loss of image information in the reduction to 8 bit (256) gray values and the compression used in JPEG. Original Digital Imaging and Communications in Medicine (DICOM) data would have been better, but was unavailable in this study.

The independent human reader; the principle investigator of this study, Dr Mahomed, scored the chest X-rays to compare the performance of independent human reader vs CAD4WHOKids.

However, Dr Mahomed was involved in the consensus 3 reader interpretation of chest X-rays, which was used as the reference standard in this study. Although the cases were read blindly, this may have resulted in recall bias for the estimated human performance.

The CAD4WHOKids was tested against the radiologist consensus reading as the reference standard, which is currently what is described in the literature on CAD on chest X-rays (127, 130, 132, 134). However a more novel approach would be comparing the performance of CAD4WHOKids software on chest X-rays against a radiological reference standard like CT chest or MRI chest. The children in our study were only imaged with chest X-rays, hence this was not done.

The software CAD4WHOKids was tested on chest X-rays from a single study centre. The application of CAD4WHOKids from chest X-rays from multiple different centres, would test the robustness of this software on textural analysis.

10.5 Future Work on Computer Aided Diagnosis on chest X-ray-CAD4WHOKids

Lung fields were manually adjusted where needed in 37% (237/644) of chest X-rays. However the aim of phase 1 of this study was to investigate if CAD4WHOKids texture analysis could identify areas of CXR-PEP vs other infiltrate or non CXR-PEP. It was challenging for the software to automatically segment lung fields; due to variability in mediastinal size on chest X-ray in children less than 5 years (25, 170, 171). To improve automatic lung field segmentation larger training sets of chest X-rays from children under 5 years are required.

As part of a post-doctoral research project Dr Mahomed was awarded the Robert Austrian Research Award in Pneumococcal Vaccinology 2016 for Post-Doctoral Research ie: phase 2 and

3 of Computer Aided Diagnosis for WHO Standardized Chest X-ray Interpretation in Children. Dr Mahomed will continue the collaboration and spend time at Radboud UMC, The Netherlands, working on the phase 2 of CAD4WHOKids which involves optimizing automated lung field segmentation. For this phase the chest X-ray data base from 3508 children enrolled in the case control study will be used. It is based on evaluating the effectiveness of pneumococcal conjugate vaccine against presumed bacterial pneumonia in hospitalized South African children in 3 public hospitals (Soweto, Cape Town and KwaZulu-Natal) (125). During this phase it would be important to integrate the WHO CRES definition clarifications, as per meeting 23-24 June 2016. Important work in this field would also be to compare the performance of CAD4WHOKids software on chest X-rays against a radiological reference standard like CT chest or MRI chest.

For phase 3, once the software CAD4WHOKids has been optimized, the chest X-ray data base from the South African PCV-9 study (16) will be accessed, and CAD4WHOKids software will be used to determine the vaccine efficacy for chest X-ray confirmed pneumonia , based on World Health Organization (WHO) standardized interpretation criteria for CXR-PEP (15) in order to validate this software.

11 Conclusion of this PhD Thesis

11.1 Objective 1

Chest X-ray quality optimization is important for accurate diagnostic purposes and conforming to Image Gently campaigns and ALARA principles in children (21, 22, 24, 25) . We found that collimation performed the worse of the 6 chest X-ray quality assessment parameters, in keeping with the literature (23), where collimation was sub-optimal in both departments with paediatric radiology expertise and departments without paediatric radiology expertise (21). This may be due to the use of wide collimation when children are moving and uncooperative (21). Hence thyroid and gonadal shielding may be important when imaging children. Education of clinicians in ordering the most suitable radiological investigation and avoiding babygrams is also very important, as was demonstrated in our study.

Combining the results of all 9 sites, for each of the 5 parameters, a low percentage was assessed as bad, while motion was present in 0-23% of chest X-rays. Chest X-ray quality assurance intervention was applied in each of the 9 sites over the 14 month period, with 3 sites demonstrating a significant improvement in chest X-ray quality and none of the other sites demonstrating a significant worsening in chest X-ray quality, using a test for trend analyses.

Recommendations from this study include pairing radiographers with experience in imaging of children with less experienced radiographers, which is important in order to train junior staff in optimizing chest X-ray quality. Where possible, all radiographs in children should be reported by radiologists with real time feedback on quality to radiographers. Ensuring that all radiographic equipment is functioning optimally is important to obtain good quality radiographs.

11.2 Objective 2, 3 and 4

In the era of routine national immunization for HiB and PCV, CXR-PEP predominantly due to due to air space disease remains the most common (33%-60%) chest X-ray abnormality in HIV-unexposed, HEU and HIV-infected children under 5 years of age hospitalized with WHO-defined severe or very severe pneumonia. These findings suggest that bacterial pneumonia, using CXR-PEP as a proxy measure thereof, remains a major contributor of hospitalization for childhood pneumonia in settings such as South Africa where PCV immunization is included in the public immunization program, even though the hospitalizations for all cause pneumonia may have decreased in the study population post PCV introduction (154).

Majority of the HIV-infected children had severe immune suppression, and were twice as likely to have CXR-PEP and less likely to have normal chest X-ray compared to HIV-unexposed children. Intrathoracic lymphadenopathy was prevalent in 14-17% of children and bilateral air trapping in 14-19% of children, with no significant difference between the 3 HIV-exposure groups. Radiographic evidence of chronic lung disease and cardiomegaly were uncommon in all 3 HIV-exposure groups.

Using a multivariate analyses model in children hospitalized with WHO-defined severe or very severe pneumonia, clinical features independently associated with presence of CXR-PEP included the presence of severe malnutrition, fever and CRP $\geq$ 40mg/dL. The presence of CXR-PEP was also associated with poor prognostic outcomes i.e.: greater need for mechanical ventilation and the composite outcome of mechanical ventilation or death. However there was no single clinical or laboratory parameter that had both high sensitivity and specificity, to

discriminate between CXR-PEP from non CXR-PEP cases, regardless of HIV-exposure status, consistent with the findings of the recent meta-analysis by Rambaud-Althaus *et al* (82).

Conversely among children with WHO-defined severe or very severe pneumonia, cases in whom the chest X-ray was evaluated as being normal were less likely to present with fever, tachypnea or to have CRP $\geq$40mg/dL. Furthermore, cases with a normal chest X-ray were also less likely to have poor prognostic outcomes i.e.: require mechanical ventilation or fulfil the composite outcome of mechanical ventilation or death.

Post national immunization for PCV vaccines in South African children, HIV-unexposed children with a PQA model probability index $\geq$ 0.5 for bacterial etiology had 2-fold greater odds for CXR-PEP compared to non CXR-PEP, and similarly HIV-unexposed children with MCPP had 3-fold greater odds of CXR-PEP compared to non CXR-PEP cases which is consistent with the literature that air space/alveolar consolidation is associated with bacterial infection (65, 69).

However in all 3 HIV-exposure groups, the sensitivity of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for bacterial etiology and MCPP was low, with a low positive predictive value, but higher specificity and a high negative predictive value. This supports the literature from previous Hib and PCV clinical trials that CXR-PEP is more specific, rather than sensitive for demonstrating bacterial vaccine efficacy (17, 161, 162), using WHO-defined standardized chest X-ray interpretation methods (15). Our study findings supports previous literature that WHO-defined CXR-PEP may under-estimated the burden of pneumonia prevented by HibCV and PCV vaccination, especially in a high HIV prevalence setting (16, 123). This may support the proposal by Madhi *et al* of the inclusion of other infiltrate with a raised CRP$\geq$40 mg/dL as an

end-point when evaluating PCV efficacy, which may assist in capturing bacterial pneumonia cases without evidence of CXR-PEP (122).

HIV-infected children with a PQA model probability index $\geq$ 0.5 for respiratory viral etiology and PQA model probability index $\geq$ 0.5 for *Pneumocystis jiroveci* etiology trended to have a greater odds for CXR-PEP vs non CXR-PEP. The sensitivities of CXR-PEP in predicting PQA model probability index $\geq$ 0.5 for being designated as respiratory viral etiology and PQA model probability index $\geq$ 0.5 for being designated as *Pneumocystis jiroveci* etiology was high, but had low positive predictive values, lower specificities and a high negative predictive values. This supports literature that CXR-PEP is of limited use in HIV-infected children as an outcome measure in PCV and other bacterial vaccine impact studies, due to opportunistic infections like *Pneumocystis jiroveci* pneumonia and respiratory viral infections contributing to CXR-PEP (62, 122, 163).

The different epidemiological settings of childhood pneumonia described in the literature including differences with regards to HIV prevalence, median age of children included in different studies, national immunization programs for HiBCV and PCV vaccines, malnutrition prevalence, disease severity, timing of hospitalization and prior antibiotic usage; all of which are important factors to consider when comparing our study findings to the literature (60-62, 104, 122, 153). The lack of standardized reporting in the definition of "chest X-ray pneumonia" in studies is also very important, as a number of studies did not differentiate in their methodology between air space/alveolar consolidation and interstitial infiltrate on chest X-ray (71, 73, 77-81).

11.3 Objective 5

The novel software CAD4WHOKids texture analysis has both high sensitivity and specificity for identifying WHO-defined CXR-PEP and differentiating from other infiltrate and non CXR-PEP in children under 5 years. Furthermore, we showed that HIV-exposure status did not materially affect the CAD4WHOKids interpretation of chest X-rays, even though the percentage of CXR-PEP in each of the HIV-exposure groups varied from 33% to 60%. A strength of this study was the large sample size of 858 children, compared to other studies, where the number of features used for classification or feature selection on CAD chest X-rays exceeded the number of chest X-rays with abnormalities. CAD4WHOKids software performed better than the inter observer agreement by human interpretation as described in the literature using standardized chest X-ray definitions (119-121).

It was challenging for CAD4WHOKids to automatically segment lung fields; due to variability in mediastinal size on chest X-ray in children less than 5 years (25, 170, 171). To improve automatic lung field segmentation larger training sets of chest X-rays from children under 5 years are required and will be addressed in phase 2 of this project.

11.4 Unifying Conclusion

Radiographic errors in paediatric chest X-rays are highlighted because they contribute to increasing the difficulty in making a diagnosis, and are more likely to be unsatisfactory in paediatric patients due to incorrect exposure factors, poor positioning and poor immobilization (22, 151, 152). Chest X-ray quality optimization is imperative for accurate diagnostic purposes and minimizing radiation in children. Our study demonstrated that chest X-ray quality was

suboptimal in 9 resource limited settings, (7 countries) in children hospitalized for WHO defined severe or very severe pneumonia. The findings and recommendations from this study on chest X-ray quality assessment and optimization will be presented to the WHO Chest Radiography in Epidemiological Studies (CRES) committee and implemented in future WHO CRES guidelines.

CXR-PEP remains the most common chest X-ray abnormality in HIV-unexposed, HEU and HIV-infected children under 5 years of age hospitalized for WHO-defined severe or very severe pneumonia, even in the era of routine HiB and PCV immunization. Our findings support the literature that CXR-PEP is of limited use in HIV-infected children as an outcome measure in bacterial vaccine impact studies, due to opportunistic infections like *Pneumocystis jiroveci* pneumonia and respiratory viral infections contributing to CXR-PEP.

HIV-unexposed children with bacterial etiology, based on PQA model probability index $\geq$ 0.5 and MCCP, had greater odds for CXR-PEP compared to non CXR-PEP. However CXR-PEP was predominantly due to respiratory viral etiology i.e.: 15% of HIV-unexposed children with a PQA model probability index $\geq$ 0.5 for bacterial etiology had CXR-PEP, while 50% of children with a PQA model probability index $\geq$ 0.5 for respiratory viral etiology had CXR-PEP. The sensitivity and positive predictive value of CXR-PEP in predicting PQA model probability index $\geq$ 0.5, $\geq$ 0.6 and $\geq$ 0.7 for bacterial etiology and MCPP was low. Hence the diagnostic utility of chest X-rays in HIV-unexposed children less than 5 years of age hospitalized with community acquired pneumonia in the era post bacterial conjugate vaccines may be limited in determining etiology in the clinical setting. The caveat is that to date a clinically acceptable gold standard for the microbiological diagnosis of bacterial pneumonia has not yet been developed. However the specificity and negative predictive value of CXR-PEP in predicting PQA model probability index $\geq$ 0.5, $\geq$ 0.6 and $\geq$ 0.7 for bacterial etiology and MCPP was high. This is important for

bacterial vaccine efficacy trials, in which the WHO standardized definition for chest X-ray endpoint emphasizes specificity, with the aim to establish whether the vaccine has activity to prevent pneumococcal or *Haemophilus influenzae* type b pneumonia in HIV-unexposed children.

Computer aided diagnosis is promising as a diagnostic tool for identifying WHO defined CXR-PEP in bacterial vaccine efficacy trials and pneumonia epidemiological studies. CAD may have an important role, especially in resource limited settings where there is limited radiologists and clinical expertise in the interpretation of paediatric chest X-rays using WHO standardized methodology (15). Further multicentre studies with large sample sizes are required for optimization and validation of this software CAD4WHOKids.

12 References

(1) Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010 Jun 5;375(9730):1969-87.

(2) Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015 Jan 31;385(9966):430-40.

(3) Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Jan 10;385(9963):117-71.

(4) O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet. 2009 Sep 12;374(9693):893-902.

(5) Watt JP, Wolfson LJ, O'Brien KL, et al. Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. Lancet. 2009 Sep 12;374(9693):903-11.

(6) Wahl B, O'Brien KL, Greenbaum A, et al. Global burden of Streptococcus pneumoniae in children younger than 5 years in the era of pneumococcal conjugate vaccines (PCV): 2000-2015. 10th International Symposium on Pneumococci and Pneumococcal Disease, Glasgow, Scotland, June 27-30 2016.

(7) Madhi SA, De Wals P, Grijalva CG, et al. The burden of childhood pneumonia in the developed world: a review of the literature. Pediatr Infect Dis J. 2013 Mar;32(3):e119-27.

(8) Daltro P, Santos EN, Gasparetto TD, et al. Pulmonary infections. Pediatr Radiol. 2011 May;41 Suppl 1:S69-82.

(9) Westra SJ, Choy G. What imaging should we perform for the diagnosis and management of pulmonary infections? Pediatr Radiol. 2009 Apr;39 Suppl 2:S178-83.

(10) Cao AM, Choy JP, Mohanakrishnan LN, et al. Chest radiographs for acute lower respiratory tract infections. Cochrane Database Syst Rev. 2013;12:CD009119.

(11) Guerra M, Crichiutti G, Pecile P, et al. Ultrasound detection of pneumonia in febrile children with respiratory distress: a prospective study. Eur J Pediatr. 2016 Feb;175(2):163-70.

(12) Chavez MA, Naithani N, Gilman RH, et al. Agreement Between the World Health Organization Algorithm and Lung Consolidation Identified Using Point-of-Care Ultrasound for the Diagnosis of Childhood Pneumonia by General Practitioners. Lung. 2015 Aug;193(4):531-8.

(13) Copetti R, Cattarossi L. Ultrasound diagnosis of pneumonia in children. Radiol Med. 2008 Mar;113(2):190-8.

(14) Pitcher RD, Lombard C, Cotton MF, et al. Clinical and immunological correlates of chest X-ray abnormalities in HIV-infected South African children with limited access to anti-retroviral therapy. Pediatr Pulmonol. 2013. Jun;49(6):581-8.

(15) Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ. 2005 May;83(5):353-9.

(16) Madhi SA, Kuwanda L, Cutland C, et al. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. Clin Infect Dis. 2005 May 15;40(10):1511-8.

(17) Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005 Mar 26-Apr 1;365(9465):1139-46.

(18) Hansen J, Black S, Shinefield H, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. Pediatr Infect Dis J. 2006 Sep;25(9):779-81.
(19) Lucero MG, Nohynek H, Williams G, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial. Pediatr Infect Dis J. 2009 Jun;28(6):455-62.
(20) World Health Organization. Pneumococcal Conjugate Vaccine for Childhood Immunization-WHO Position Paper. Weekly epidemiological record. 2007;82: 93–104.
(21) Alt CD, Engelmann D, Schenk JP, et al. [Quality control of thoracic X-rays in children in diagnostic centers with and without pediatric-radiologic competence]. Rofo. 2006 Feb;178(2):191-9.
(22) Cook JV, Kyriou JC, Pettet A, et al. Key factors in the optimization of paediatric X-ray practice. Br J Radiol. 2001 Nov;74(887):1032-40.
(23) Hlabangana LT, Andronikou S. Short-term impact of pictorial posters and a crash course on radiographic errors for improving the quality of paediatric chest radiographs in an unsupervised unit - a pilot study for quality-assurance outreach. Pediatr Radiol. 2015 Feb;45(2):158-165.
(24) Strauss KJ, Goske MJ, Kaste SC, et al. Image gently: Ten steps you can take to optimize image quality and lower CT dose for pediatric patients. AJR Am J Roentgenol. 2010 Apr;194(4):868-73.
(25) Menashe SJ, Iyer RS, Parisi MT, et al. Pediatric Chest Radiographs: Common and Less Common Errors. AJR Am J Roentgenol. 2016 Aug 4:1-9.
(26) Guo H, Liu WY, He XY, et al. Optimizing imaging quality and radiation dose by the age-dependent setting of tube voltage in pediatric chest digital radiography. Korean J Radiol. 2013 Jan-Feb;14(1):126-31.
(27) Don S, Macdougall R, Strauss K, et al. Image gently campaign back to basics initiative: ten steps to help manage radiation dose in pediatric digital radiography. AJR Am J Roentgenol. 2013 May;200(5):W431-6.
(28) Willis CE. Optimizing digital radiography of children. Eur J Radiol. 2009 Nov;72(2):266-73.
(29) Kohda E, Tsutsumi Y, Nagamoto M, et al. Revisit image control for pediatric chest radiography. Radiat Med. 2007 Feb;25(2):60-4.
(30) Global report: UNAIDS report on the global AIDS epidemic 2013. Joint United Nations Programme on HIV/AIDS (UNAIDS). ISBN 978-92-9253-032-7.
(31) Zar HJ, Madhi SA. Childhood pneumonia--progress and challenges. S Afr Med J. 2006 Sep;96(9 Pt 2):890-900.
(32) McNally LM, Jeena PM, Gajee K, et al. Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study. Lancet. 2007 Apr 28;369(9571):1440-51.
(33) Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. JAMA. 2006 Jul 19;296(3):292-300.
(34) Madhi SA, Petersen K, Madhi A, et al. Impact of human immunodeficiency virus type 1 on the disease spectrum of Streptococcus pneumoniae in South African children. Pediatr Infect Dis J. 2000 Dec;19(12):1141-7.
(35) Aliyu MH, Salihu HM. Tuberculosis and HIV disease: two decades of a dual epidemic. Wien Klin Wochenschr. 2003 Oct 31;115(19-20):685-97.
(36) Donald PR. Childhood tuberculosis: out of control? Curr Opin Pulm Med. 2002 May;8(3):178-82.
(37) Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. Pediatr Pulmonol. 2008 Jan;43(1):1-10.

(38) Dangor Z, Izu A, Hillier K, et al. Impact of the antiretroviral treatment program on the burden of hospitalization for culture-confirmed tuberculosis in South African children: a time-series analysis. Pediatr Infect Dis J. 2013 Sep;32(9):972-7.
(39) Moore DP, Klugman KP, Madhi SA. Role of Streptococcus pneumoniae in hospitalization for acute community-acquired pneumonia associated with culture-confirmed Mycobacterium tuberculosis in children: a pneumococcal conjugate vaccine probe study. Pediatr Infect Dis J. 2010 Dec;29(12):1099-04.
(40) Afran L, Garcia Knight M, Nduati E, et al. HIV-exposed uninfected children: a growing population with a vulnerable immune system? Clin Exp Immunol. 2014 Apr;176(1):11-22.
(41) von Mollendorf C, Von Gottberg A, Tempia S, et al. Increased Risk for and Mortality From Invasive Pneumococcal Disease in HIV-Exposed but Uninfected Infants Aged <1 Year in South Africa, 2009-2013. Clin Infect Dis. 2015. May 1;60(9):1346-56.
(42) Koyanagi A, Humphrey JH, Ntozini R, et al. Morbidity among human immunodeficiency virus-exposed but uninfected, human immunodeficiency virus-infected, and human immunodeficiency virus-unexposed infants in Zimbabwe before availability of highly active antiretroviral therapy. Pediatr Infect Dis J. 2011 Jan;30(1):45-51.
(43) Kourtis AP, Wiener J, Kayira D, et al. Health outcomes of HIV-exposed uninfected African infants. AIDS. 2013 Mar 13;27(5):749-59.
(44) Reikie BA, Naidoo S, Ruck CE, et al. Antibody responses to vaccination among South African HIV-exposed and unexposed uninfected infants during the first 2 years of life. Clin Vaccine Immunol. 2013 Jan;20(1):33-8.
(45) Cohen C, von Mollendorf C, de Gouveia L, et al. Effectiveness of 7-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in HIV-infected and -uninfected children in south africa: a matched case-control study. Clin Infect Dis. 2014 Sep 15;59(6):808-18.
(46) Madhi SA, Adrian P, Cotton MF, et al. Effect of HIV infection status and anti-retroviral treatment on quantitative and qualitative antibody responses to pneumococcal conjugate vaccine in infants. J Infect Dis. 2010 Aug 15;202(3):355-61.
(47) Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011 Oct;53(7):e25-76.
(48) Andronikou S, McHugh K, Abdurahman N, et al. Paediatric radiology seen from Africa. Part I: providing diagnostic imaging to a young population. Pediatr Radiol. 2011 Jul;41(7):811-25.
(49) Correia MA, Mello MJ, Petribu NC, et al. Agreement on radiological diagnosis of acute lower respiratory tract infection in children. J Trop Pediatr. 2011 Jun;57(3):204-7.
(50) Sarria E, Fischer GB, Lima JA, et al. [Interobserver agreement in the radiological diagnosis of lower respiratory tract infections in children]. J Pediatr (Rio J). 2003 Nov-Dec;79(6):497-503.
(51) Albaum MN, Hill LC, Murphy M, et al. Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. Chest. 1996 Aug;110(2):343-50.
(52) Williams GJ, Macaskill P, Kerr M, et al. Variability and accuracy in interpretation of consolidation on chest radiography for diagnosing pneumonia in children under 5 years of age. Pediatr Pulmonol. 2013 Dec;48(12):1195-200.
(53) Korppi M, Don M, Valent F, et al. The value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children. Acta Paediatr. 2008 Jul;97(7):943-7.
(54) Glezen P, Denny FW. Epidemiology of acute lower respiratory disease in children. N Engl J Med. 1973 Mar 8;288(10):498-505.
(55) Borrero I, Fajardo L, Bedoya A, et al. Acute respiratory tract infections among a birth cohort of children from Cali, Colombia, who were studied through 17 months of age. Rev Infect Dis. 1990 Nov-Dec;12 Suppl 8:S950-6.
(56) Lepage P, Munyakazi C, Hennart P. Breastfeeding and hospital mortality in children in Rwanda. Lancet. 1981 Aug 22;2(8243):409-11.

(57) Rochester DF, Esau SA. Malnutrition and the respiratory system. Chest. 1984 Mar;85(3):411-5.
(58) Tupasi TE, Mangubat NV, Sunico ME, et al. Malnutrition and acute respiratory tract infections in Filipino children. Rev Infect Dis. 1990 Nov-Dec;12 Suppl 8:S1047-54.
(59) Key NK, Araujo-Neto CA, Cardoso M, et al. Characteristics of radiographically diagnosed pneumonia in under-5 children in Salvador, Brazil. Indian Pediatr. 2011 Nov 11;48(11):873-7.
(60) Ferrero F, Nascimento-Carvalho CM, Cardoso MR, et al. Radiographic findings among children hospitalized with severe community-acquired pneumonia. Pediatr Pulmonol. 2010 Oct;45(10):1009-13.
(61) Bharti B, Kaur L, Bharti S. Role of chest X-ray in predicting outcome of acute severe pneumonia. Indian Pediatr. 2008 Nov;45(11):893-8.
(62) Madhi SA, Cumin E, Klugman KP. Defining the potential impact of conjugate bacterial polysaccharide-protein vaccines in reducing the burden of pneumonia in human immunodeficiency virus type 1-infected and -uninfected children. Pediatr Infect Dis J. 2002 May;21(5):393-9.
(63) Don M, Valent F, Korppi M, et al. Differentiation of bacterial and viral community-acquired pneumonia in children. Pediatr Int. 2009 Feb;51(1):91-6.
(64) Wahlgren H, Mortensson W, Eriksson M, et al. Radiological findings in children with acute pneumonia: age more important than infectious agent. Acta Radiol. 2005 Jul;46(4):431-6.
(65) Virkki R, Juven T, Rikalainen H, et al. Differentiation of bacterial and viral pneumonia in children. Thorax. 2002 May;57(5):438-41.
(66) Kelly MS, Crotty EJ, Rattan MS, et al. Chest Radiographic Findings and Outcomes of Pneumonia Among Children in Botswana. Pediatr Infect Dis J. 2016 Mar;35(3):257-62.
(67) Jeena PM, Minkara AK, Corr P, et al. Impact of HIV-1 status on the radiological presentation and clinical outcome of children with WHO defined community-acquired severe pneumonia. Arch Dis Child. 2007 Nov;92(11):976-9.
(68) Esposito S, Bosis S, Cavagna R, et al. Characteristics of Streptococcus pneumoniae and atypical bacterial infections in children 2-5 years of age with community-acquired pneumonia. Clin Infect Dis. 2002 Dec 1;35(11):1345-52.
(69) Korppi M, Kiekara O, Heiskanen-Kosma T, et al. Comparison of radiological findings and microbial aetiology of childhood pneumonia. Acta Paediatr. 1993 Apr;82(4):360-3.
(70) Ayalon I, Glatstein MM, Zaidenberg-Israeli G, et al. The role of physical examination in establishing the diagnosis of pneumonia. Pediatr Emerg Care. 2013 Aug;29(8):893-6.
(71) Lynch T, Platt R, Gouin S, et al. Can we predict which children with clinically suspected pneumonia will have the presence of focal infiltrates on chest radiographs? Pediatrics. 2004 Mar;113(3 Pt 1):e186-9.
(72) Dai Y, Foy HM, Zhu Z, et al. Respiratory rate and signs in roentgenographically confirmed pneumonia among children in China. Pediatr Infect Dis J. 1995 Jan;14(1):48-50.
(73) Zukin DD, Hoffman JR, Cleveland RH, et al. Correlation of pulmonary signs and symptoms with chest radiographs in the pediatric age group. Ann Emerg Med. 1986 Jul;15(7):792-6.
(74) Renoult E, Buteau C, Turgeon N, et al. Is routine chest radiography necessary for the initial evaluation of fever in neutropenic children with cancer? Pediatr Blood Cancer. 2004 Sep;43(3):224-8.
(75) Zimmerman DR, Kovalski N, Fields S, et al. Diagnosis of childhood pneumonia: clinical assessment without radiological confirmation may lead to overtreatment. Pediatr Emerg Care. 2012 Jul;28(7):646-9.
(76) Wilkins TR, Wilkins RL. Clinical and radiographic evidence of pneumonia. Radiol Technol. 2005 Nov-Dec;77(2):106-10.
(77) Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. Clin Pediatr (Phila). 1982 Dec;21(12):730-4.
(78) Palafox M, Guiscafre H, Reyes H, et al. Diagnostic value of tachypnoea in pneumonia defined radiologically. Arch Dis Child. 2000 Jan;82(1):41-5.

(79) Rothrock SG, Green SM, Fanelli JM, et al. Do published guidelines predict pneumonia in children presenting to an urban ED? Pediatr Emerg Care. 2001 Aug;17(4):240-3.
(80) Wingerter SL, Bachur RG, Monuteaux MC, et al. Application of the world health organization criteria to predict radiographic pneumonia in a US-based pediatric emergency department. Pediatr Infect Dis J. 2012 Jun;31(6):561-4.
(81) Tanen DA, Trocinski DR. The use of pulse oximetry to exclude pneumonia in children. Am J Emerg Med. 2002 Oct;20(6):521-3.
(82) Rambaud-Althaus C, Althaus F, Genton B, et al. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. Lancet Infect Dis. 2015 Apr;15(4):439-50.
(83) McClain L, Hall M, Shah SS, et al. Admission chest radiographs predict illness severity for children hospitalized with pneumonia. J Hosp Med. 2014 Sep;9(9):559-64.
(84) Grafakou O, Moustaki M, Tsolia M, et al. Can chest X-ray predict pneumonia severity? Pediatr Pulmonol. 2004 Dec;38(6):465-9.
(85) Eriksson J, Nordshus T, Carlsen KH, et al. Radiological findings in children with respiratory syncytial virus infection: relationship to clinical and bacteriological findings. Pediatr Radiol. 1986;16(2):120-2.
(86) Friis B, Eiken M, Hornsleth A, et al. Chest X-ray appearances in pneumonia and bronchiolitis. Correlation to virological diagnosis and secretory bacterial findings. Acta Paediatr Scand. 1990 Feb;79(2):219-25.
(87) Wahlgren H, Eriksson M, Mortensson W, et al. Isolation of pathogenic bacteria from the nasopharynx of children with respiratory syncytial virus infection. Predictive value of chest roentgen examination and laboratory tests. Scand J Infect Dis. 1984;16(2):139-43.
(88) Swingler GH. Radiologic differentiation between bacterial and viral lower respiratory infection in children: a systematic literature review. Clin Pediatr (Phila). 2000 Nov;39(11):627-33.
(89) Swischuk LE, Hayden CK, Jr. Viral vs. bacterial pulmonary infections in children (is roentgenographic differentiation possible?). Pediatr Radiol. 1986;16(4):278-84.
(90) Pornkul R, Suwanjutha S, Ruangkanchanasetr S. Correlation of roentgenologic diagnosis and etiologic agents of pneumonia in thai children under 5 years of age. J Med Assoc Thai. 1993 Oct;76 Suppl 2:178-86.
(91) Bettenay FA, de Campo JF, McCrossin DB. Differentiating bacterial from viral pneumonias in children. Pediatr Radiol. 1988;18(6):453-4.
(92) Courtoy I, Lande AE, Turner RB. Accuracy of radiographic differentiation of bacterial from nonbacterial pneumonia. Clin Pediatr (Phila). 1989 Jun;28(6):261-4.
(93) McCarthy PL, Spiesel SZ, Stashwick CA, et al. Radiographic findings and etiologic diagnosis in ambulatory childhood pneumonias. Clin Pediatr (Phila). 1981 Nov;20(11):686-91.
(94) Cevey-Macherel M, Galetto-Lacour A, Gervaix A, et al. Etiology of community-acquired pneumonia in hospitalized children based on WHO clinical guidelines. Eur J Pediatr. 2009 Dec;168(12):1429-36.
(95) Nascimento-Carvalho CM, Alves NN, Athayde LA, et al. Is there any association of a specific chest X-ray pattern and bacteremia in children with penumonia? J Trop Pediatr. 2002 Aug;48(4):253-4.
(96) Vuori-Holopainen E, Salo E, Saxen H, et al. Etiological diagnosis of childhood pneumonia by use of transthoracic needle aspiration and modern microbiological methods. Clin Infect Dis. 2002 Mar 1;34(5):583-90.
(97) Vuori-Holopainen E, Peltola H. Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia. Clin Infect Dis. 2001 Mar 1;32(5):715-26.
(98) Lynch T, Bialy L, Kellner JD, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. PLoS One. 2010;5(8):e11989.
(99) George R, Andronikou S, Theron S, et al. Pulmonary infections in HIV-positive children. Pediatr Radiol. 2009 Jun;39(6):545-54.

(100) Jeena PM, Coovadia HM, Thula SA, et al. Persistent and chronic lung disease in HIV-1 infected and uninfected African children. AIDS. 1998 Jul 9;12(10):1185-93.
(101) Marais BJ, Gie RP, Schaaf HS, et al. Childhood pulmonary tuberculosis: old wisdom and new challenges. Am J Respir Crit Care Med. 2006 May 15;173(10):1078-90.
(102) Zar HJ. Diagnosis of pulmonary tuberculosis in children--what's new? S Afr Med J. 2007 Oct;97(10 Pt 2):983-5.
(103) Marais BJ. Childhood tuberculosis--risk assessment and diagnosis. S Afr Med J. 2007 Oct;97(10 Pt 2):978-82.
(104) Pitcher RD, Lombard CJ, Cotton MF, et al. Chest radiographic abnormalities in HIV-infected African children: a longitudinal study. Thorax. 2015. Sep;70(9):840-6.
(105) Andronikou S, DJ vdM, Goussard P, et al. Usefulness of lateral radiographs for detecting tuberculous lymphadenopathy in children- confirmation using sagittal CT reconstruction with multiplanar cross-referencing. SAJR. 2012;16(3):87-92.
(106) SA National Department of Health. Guidelines for the Management of HIV in Children. 2nd edition ed 2010. familymedicine.ukzn.ac.za/Libraries/Guidelines.../2010_Paediatric_Guidelines.pdf.
(107) Leung AN, Muller NL, Pineda PR, et al. Primary tuberculosis in childhood: radiographic manifestations. Radiology. 1992 Jan;182(1):87-91.
(108) Andronikou S, Joseph E, Lucas S, et al. CT scanning for the detection of tuberculous mediastinal and hilar lymphadenopathy in children. Pediatr Radiol. 2004 Mar;34(3):232-6.
(109) Pitcher RD, Beningfield SJ, Zar HJ. The chest X-ray features of chronic respiratory disease in HIV-infected children - a review. Paediatr Respir Rev. 2015. Sep;16(4):258-66.2015.
(110) Du Toit G, Swingler G, Iloni K. Observer variation in detecting lymphadenopathy on chest radiography. Int J Tuberc Lung Dis. 2002 Sep;6(9):814-7.
(111) Milkovic D, Richter D, Zoricic-Letoja I, et al. Chest radiography findings in primary pulmonary tuberculosis in children. Coll Antropol. 2005 Jun;29(1):271-6.
(112) Kim WS, Moon WK, Kim IO, et al. Pulmonary tuberculosis in children: evaluation with CT. AJR Am J Roentgenol. 1997 Apr;168(4):1005-9.
(113) Schaaf HS, Marais BJ, Whitelaw A, et al. Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. BMC Infect Dis. 2007;7:140.
(114) Srinakarin J, Roongpittayanon N, Teeratakulpisarn J, et al. Comparison between the radiographic findings in pulmonary tuberculosis of children with or without HIV infection. J Med Assoc Thai. 2012 Jun;95(6):802-8.
(115) Du Plessis V, Andronikou S, Struck G, et al. Baseline chest radiographic features of HIV-infected children eligible for antiretroviral therapy. S Afr Med J. 2011 Nov;101(11):829-34.
(116) Kouakoussui A, Fassinou P, Anaky MF, et al. Respiratory manifestations in HIV-infected children pre- and post-HAART in Abidjan, the Ivory Coast. Paediatr Respir Rev. 2004 Dec;5(4):311-5.
(117) Norton KI, Kattan M, Rao JS, et al. Chronic radiographic lung changes in children with vertically transmitted HIV-1 infection. AJR Am J Roentgenol. 2001 Jun;176(6):1553-8.
(118) Sheikh S, Madiraju K, Steiner P, et al. Bronchiectasis in pediatric AIDS. Chest. 1997 Nov 5;112(5):1202-7.
(119) Patel AB, Amin A, Sortey SZ, et al. Impact of training on observer variation in chest radiographs of children with severe pneumonia. Indian Pediatr. 2007 Sep;44(9):675-81.
(120) Hib Initiative Radiology Workshop; 2011 11-12 October 2011; Hanoi, Vietnam
(121) Elemraid MA, Muller M, Spencer DA, et al. Accuracy of the interpretation of chest radiographs for the diagnosis of paediatric pneumonia. PLoS One. 2014;9(8):e106051.
(122) Madhi SA, Klugman KP. World Health Organisation definition of "radiologically-confirmed pneumonia" may under-estimate the true public health value of conjugate pneumococcal vaccines. Vaccine. 2007 Mar 22;25(13):2413-9.

(123) Mahomed N, Madhi SA. Radiologic diagnosis of chest infection in children: WHO end-point consolidation. Pediatr Radiol. 2014 Jun;44(6):685-6.
(124) Griffin MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med. 2013 Jul 11;369(2):155-63.
(125) Madhi SA, Groome MJ, Zar HJ, et al. Effectiveness of pneumococcal conjugate vaccine against presumed bacterial pneumonia hospitalisation in HIV-uninfected South African children: a case-control study. Thorax. 2015. Dec;70(12):1149-55.
(126) WHO Short and Long-term PCV Impact Evaluation; 2013 10-12 September 2013; Geneva, Switzerland.
(127) Mouton A, Pitcher RD, Douglas TS. Computer-aided detection of pulmonary pathology in pediatric chest radiographs. Med Image Comput Comput Assist Interv. 2010;13(Pt 3):619-25.
(128) Xu T, Mandal M, Long R, et al. An edge-region force guided active shape approach for automatic lung field detection in chest radiographs. Comput Med Imaging Graph. 2012 Sep;36(6):452-63.
(129) van Ginneken B, ter Haar Romeny BM, Viergever MA. Computer-aided diagnosis in chest radiography: a survey. IEEE Trans Med Imaging. 2001 Dec;20(12):1228-41.
(130) van Ginneken B, Katsuragawa S, ter Haar Romeny BM, et al. Automatic detection of abnormalities in chest radiographs using local texture analysis. IEEE Trans Med Imaging. 2002 Feb;21(2):139-49.
(131) Arzhaeva Y, Hogeweg L, de Jong PA, et al. Global and local multi-valued dissimilarity-based classification: application to computer-aided detection of tuberculosis. Med Image Comput Comput Assist Interv. 2009;12(Pt 2):724-31.
(132) Oliveira LL, Silva SA, Ribeiro LH, et al. Computer-aided diagnosis in chest radiography for detection of childhood pneumonia. Int J Med Inform. 2008 Aug;77(8):555-64.
(133) van Ginneken B, Hogeweg L, Prokop M. Computer-aided diagnosis in chest radiography: beyond nodules. Eur J Radiol. 2009 Nov;72(2):226-30.
(134) Evaluation of Classifiers to a Childhood Pneumonia Computer-aided Diagnosis System, (2014).
(135) SA National Department of Health. New EPI Vaccine Guidelines. 2010 https://www.health-e.org.za/wp-content/uploads/2014/02/South-Africa-EPI-vaccines-revised-Oct-2010.pdf.
(136) Deloria-Knoll M, Feikin DR, Scott JA, et al. Identification and selection of cases and controls in the Pneumonia Etiology Research for Child Health project. Clin Infect Dis. 2012 Apr;54 Suppl 2:S117-23.
(137) Murdoch DR, O'Brien KL, Driscoll AJ, et al. Laboratory methods for determining pneumonia etiology in children. Clin Infect Dis. 2012 Apr;54 Suppl 2:S146-52.
(138) Levine OS, O'Brien KL, Deloria-Knoll M, et al. The Pneumonia Etiology Research for Child Health Project: a 21st century childhood pneumonia etiology study. Clin Infect Dis. 2012 Apr;54 Suppl 2:S93-101.
(139) Bhat N, O'Brien KL, Karron RA, et al. Use and evaluation of molecular diagnostics for pneumonia etiology studies. Clin Infect Dis. 2012 Apr;54 Suppl 2:S153-8.
(140) Scott JA, Wonodi C, Moisi JC, et al. The definition of pneumonia, the assessment of severity, and clinical standardization in the Pneumonia Etiology Research for Child Health study. Clin Infect Dis. 2012 Apr;54 Suppl 2:S109-16.
(141) Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS One. 2014;9(3):e91464.
(142) Smuts NA, Beyers N, Gie RP, et al. Value of the lateral chest radiograph in tuberculosis in children. Pediatr Radiol. 1994;24(7):478-80.
(143) European guidelines on quality criteria for diagnostic radiographic images in paediatrics. European Commission Report EUR 16261 Luxembourg:Office for Official Publications of the European Communities. 1996 https://cordis.europa.eu/pub/fp5-euratom/docs/eur16261.pdf.

(144) Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008 Mar;246(3):697-722.
(145) Algin O, Gokalp G, Topal U. Signs in chest imaging. Diagn Interv Radiol. 2011 Mar;17(1):18-29.
(146) Andronikou S, Vanhoenacker FM, De Backer AI. Advances in imaging chest tuberculosis: blurring of differences between children and adults. Clin Chest Med. 2009 Dec;30(4):717-44, viii.
(147) Who Case Definitions of HIV For Surveillance And Revised Clinical Staging And Immunological Classification Of HIV-Related Disease In Adults And Children. Geneva: WHO; 2006 WHO; 2006. www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf.
(148) Wu Z D-KM, Hammitt LL, Zeger SL. . Partially latent class models for case-control studies of childhood pneumonia aetiology. . J R Stat Soc Ser C (Applied Stat). 2016(65):97–114.
(149) Wu Z D-KM, Zeger S. . Nested Partially-Latent Class Models for Dependent Binary Data; Estimating Disease Etiology. . Biostatistics. 2016;In Press; :1-24.
(150) Veldkamp WJ, Kroft LJ, Geleijns J. Dose and perceived image quality in chest radiography. Eur J Radiol. 2009 Nov;72(2):209-17.
(151) Gallet JM, Reed MH, Hlady J. A novel quality assurance method in a university teaching paediatric radiology department. Br J Radiol. 2000 Aug;73(872):843-6.
(152) Seidenbusch MC, Schneider K. [Radiation exposure of children in pediatric radiology. Part 4: Entrance doses achieved during the X-ray examination of the chest]. Rofo. 2008 Dec;180(12):1082-103.
(153) Kin Key N, Araujo-Neto CA, Nascimento-Carvalho CM. Severity of childhood community-acquired pneumonia and chest radiographic findings. Pediatr Pulmonol. 2009 Mar;44(3):249-52.
(154) Izu A SF, Nzenze SA, Mudau A , Zell E, O'Brien K, Whitney C G, Verani J, Groome M, Madhi SA. Temporal association of pneumococcal conjugate vaccine on all-cause pneumonia hospitalization among children in Soweto, South African: a time series analysis from 2006-2014. 10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD), 26-30 June 2016 Glascow, Scotland2016. p. Poster 105.
(155) Farley JJ, King JC, Jr., Nair P, et al. Invasive pneumococcal disease among infected and uninfected children of mothers with human immunodeficiency virus infection. J Pediatr. 1994 Jun;124(6):853-8.
(156) Zar HJ, Dechaboon A, Hanslo D, et al. Pneumocystis carinii pneumonia in South African children infected with human immunodeficiency virus. Pediatr Infect Dis J. 2000 Jul;19(7):603-7.
(157) Chintu C, Mudenda V, Lucas S, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. Lancet. 2002 Sep 28;360(9338):985-90.
(158) Lala SG, Madhi SA, Pettifor JM. The discriminative value of C-reactive protein levels in distinguishing between community-acquired bacteraemic and respiratory virus-associated lower respiratory tract infections in HIV-1-infected and -uninfected children. Ann Trop Paediatr. 2002 Sep;22(3):271-9.
(159) Mulholland K, Hilton S, Adegbola R, et al. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants. Lancet. 1997 Apr 26;349(9060):1191-7.
(160) Tregnaghi MW, Saez-Llorens X, Lopez P, et al. Efficacy of pneumococcal nontypable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in young Latin American children: A double-blind randomized controlled trial. PLoS Med. 2014 Jun;11(6):e1001657.
(161) Tregnaghi MW, Sáez-Llorens X, López P, et al. Efficacy of Pneumococcal Nontypable Haemophilus influenzae Protein D Conjugate Vaccine (PHiD-CV) in Young Latin American Children: A Double-Blind Randomized Controlled Trial. PLoS Med. 2014;11(6):e1001657.
(162) Baqui AH, El Arifeen S, Saha SK, et al. Effectiveness of Haemophilus influenzae type B conjugate vaccine on prevention of pneumonia and meningitis in Bangladeshi children: a case-control study. Pediatr Infect Dis J. 2007 Jul;26(7):565-71.

(163) Klugman KP, Madhi SA, Huebner RE, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003 Oct 2;349(14):1341-8.
(164) Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. Int J Tuberc Lung Dis. 2007 Apr;11(4):417-23.
(165) Andronikou S, Brauer B, Galpin J, et al. Interobserver variability in the detection of mediastinal and hilar lymph nodes on CT in children with suspected pulmonary tuberculosis. Pediatr Radiol. 2005 Apr;35(4):425-8.
(166) Andronikou S, Wieselthaler N. Modern imaging of tuberculosis in children: thoracic, central nervous system and abdominal tuberculosis. Pediatr Radiol. 2004 Nov;34(11):861-75.
(167) Lucas S, Andronikou S, Goussard P, et al. CT features of lymphobronchial tuberculosis in children, including complications and associated abnormalities. Pediatr Radiol. 2012 Aug;42(8):923-31.
(168) Andronikou S, Wieselthaler N. Imaging for tuberculosis in children. Tuberculosis a Comprehensive Clinical Reference: Schaaf HS, Philadelphia: Saunders Elsevier 2009. Pg 36. https://pdfs.semanticscholar.org/948e/f617fda4bdffeda0d2fed5f32c3cc67af18a.pdf.
(169) van Ginneken B, Stegmann MB, Loog M. Segmentation of anatomical structures in chest radiographs using supervised methods: a comparative study on a public database. Med Image Anal. 2006 Feb;10(1):19-40.
(170) Meyers A, Shah A, Cleveland RH, et al. Thymic size on chest radiograph and rapid disease progression in human immunodeficiency virus 1-infected children. Pediatr Infect Dis J. 2001 Dec;20(12):1112-8.
(171) Mendelson DS. Imaging of the thymus. Chest Surg Clin N Am. 2001 May;11(2):269-93
(172) Hogeweg L, Sanchez C, Maduskar P, et al. Automatic detection of tuberculosis in chest radiographs using a combination of textural, focal, and shape abnormality analysis. IEEE Trans Med Imaging. 2015 Feb 19.
(173) Loog M VGB, editor. Static posterior probability fusion for signal detection: applications in the detection of interstitial diseases in chest radiographs. International Conference on Pattern Recognition; 2004.

13 Appendices

13.1 Appendix 1: Radiologic diagnosis of chest infection in children: WHO end-point consolidation

Pediatr Radiol (2014) 44:685–686
DOI 10.1007/s00247-014-2933-0

MINISYMPOSIUM

Radiologic diagnosis of chest infection in children: WHO end-point consolidation

Nasreen Mahomed · Shabir A. Madhi

Received: 18 December 2013 / Accepted: 12 February 2014
© Springer-Verlag Berlin Heidelberg 2014

Pneumonia caused by *Streptococcus pneumoniae* is the leading cause of morbidity and mortality in children younger than 5 years, with pneumococcal conjugate vaccines providing an opportunity to reduce this burden of illness [1]. In 2007 the World Health Organization (WHO) recommended global expansion of the 7-valent pneumococcal conjugate vaccine (PCV-7), with priority introduction in countries with a <5-years-old child mortality rate of >50/1,000 live births, in countries where >50,000 children die annually and in countries with a high prevalence of human immunodeficiency virus (HIV) [2].

Because radiologic diagnosis of pneumonia is used as the outcome measure in epidemiological trials, a standardized method for radiographically diagnosing pneumonia was developed by the WHO radiologic working group (initially established in 1997) to provide a consensus method for reading chest radiographs in vaccine efficacy and epidemiological trials of pneumonia [3]. End-point consolidation was defined as a dense or fluffy opacity that occupied a portion, a lobe or an entire lung, with or without air bronchograms. Primary end-point pneumonia was defined as end-point consolidation or pleural effusion involving the lateral pleural space and associated with pulmonary parenchymal infiltrate, or an effusion that "obliterated enough of the hemithorax to obscure an opacity" [3].

The 9-valent pneumococcal conjugate vaccine reduced the incidence of WHO defined chest-radiograph-confirmed pneumonia by 25% in non-HIV-infected South African children [4] and by 37% in Gambian children [5]. The pneumococcal conjugate vaccine (PCV) also reduced the incidence of vaccine serotype and antibiotic-resistant invasive pneumococcal disease among HIV-infected and non-HIV-infected South African children [6]. A post hoc analysis of the South African PCV trial, however, suggested WHO radiologic end point under-estimated the burden of pneumonia prevented by vaccination [6]. This could be attributed to the pre-determined chest radiograph end point being geared toward improved specificity, rather than sensitivity [3]. In the United States, where the introduction of childhood pneumococcal conjugate vaccine immunization has resulted in a 36% reduction in all-cause pneumonia, many children included were unlikely to have fulfilled the WHO predetermined end point of "radiologically confirmed" pneumonia [7].

The current aim of the WHO is to re-establish a radiology working group with the objective of providing a more sensitive end point for radiologically confirmed pneumonia, without compromising on specificity, with which to measure vaccine effectiveness in preventing pneumonia. This would be important in future international studies evaluating the full public health benefit of immunization with pneumococcal conjugate vaccines and pneumonia epidemiological studies.

Acknowledgments Dr Nasreen Mahomed represented the World Federation of Pediatric Imaging at the WHO meeting to discuss the end-point criteria for pneumonia.

WHO Short and Long-term PCV Impact Evaluation meeting. Geneva, Switzerland 10-12 September 2013.

Conflict of interest None

N. Mahomed (✉)
Department of Diagnostic Radiology, University of Witwatersrand, Private Bag 3, Wits, 2050 Johannesburg, South Africa
e-mail: Nasreen.Mahomed@wits.ac.za

S. A. Madhi
Medical and Research Council: Respiratory and Meningal Pathogens Research Unit, University of Witwatersrand, Private Bag 3, Wits, 2050 Johannesburg, South Africa

References

1. O'Brien KL, Wolfson LJ, Watt JP et al. (2009) Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. Lancet 374:893–902
2. World Health Organization (2007) Pneumococcal conjugate vaccine for childhood immunization- WHO position paper. Weekly epidemiological record. http://www.who.int/wer. Accessed 3 Feb 2014

3. Cherian T, Mulholland EK, Carlin JB et al (2005) Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ 83:353–359
4. Klugman KP, Madhi SA, Huebner RE et al (2003) A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 34914:1341–1348
5. Cutts FT, Zaman SMA, Enwere G et al (2005) Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in the Gambia: randomised, double-blind, placebo-controlled trial. Lancet 365:1139–1146
6. Madhi SA, Kuwanda L, Cutland C et al (2005) The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. Clin Infect Dis 40:1511–1518
7. Griffin MR, Zhu Y, Moore MR et al (2013) U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med 369:155–163

13.2 Appendix 2: Best Oral Paper University of the Witwatersrand, Faculty of Health Sciences Research Day & Postgraduate Expo, 1 September 2016, Theme 1: Clinical Sciences and Therapeutics for Health

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

Faculty Research Day and Postgraduate Expo 2016

Clinical Sciences & Therapeutics For Health

Best Oral Presentation to

Nasreen Mahomed

Professor Martin Veller
Dean: Faculty of Health Sciences

Professor Witness Mudzi
Research Day Chair

13.3 Appendix 3: Chest X-Ray Quality Assessment Customized Report Form

Site:	**Month:**					
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						

Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						

Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Image Number	Positioning	Collimation	Exposure	Motion	Inspiration	Processing
	☐ Bad	☐ Bad	☐ Bad	☐ Yes	☐ Bad	☐ Bad
	☐ Fair	☐ Fair	☐ Fair	☐ No	☐ Fair	☐ Fair
	☐ Good	☐ Good	☐ Good		☐ Good	☐ Good
Comments						
Overall Comments on chest X-ray quality						
Feedback from site: please include your response to the comments above and/or updates of the new actions to improve chest X-ray quality						

13.4 Appendix 4: Customized Detailed Chest X-Ray Reporting Form

Study Number:

Reader 1 ☐ 2 ☐ 3 ☐

Technical quality	**Acceptable**	**Uninterpretable**	**Not available**
AP	☐	☐	☐
Lateral	☐	☐	☐

Airspace disease ☐ **Y** ☐ **N**	**Zones** **R** **L** ☐ U ☐ ☐ M ☐ ☐ L ☐	☐ segmental/sub segmental consolidation ☐ lobar consolidation ☐ multi-lobar consolidation ☐ volume loss/collapse ☐ expansion/bulging fissure ☐ lung abscess

Pleural Disease ☐ **Y** ☐ **N**	**R** **L** ☐ ☐	☐ pleural effusion
	R **L** ☐ ☐	☐ pneumothorax
	R **L** ☐ ☐	☐ pleural plaques/calcification

Chest X-Ray Primary End-point Pneumonia ☐ **Y** ☐ **N** **CXR-PEP**

Other Infiltrate ☐ **Y** ☐ **N**	**Zones** **R** **L** ☐ U ☐ ☐ M ☐ ☐ L ☐	☐ peribronchial thickening
		☐ reticulo-nodular infiltrate
		☐ reticular infiltrate
		☐ miliary infiltrate (nodules < 3mm)
		☐ large nodular infiltrate (nodules > 3mm)
		☐ perihilar streakiness
		☐ ground glass infiltrate

Chronic Lung Disease ☐ **Y** ☐ **N**	**Zones** **R** **L** ☐ U ☐ ☐ M ☐ ☐ L ☐	☐ bronchiectasis
		☐ cavities
		☐ fibroses

Lymphadenopathy ☐ **Y** ☐ **N**	**R** **L** ☐ ☐	☐ hilar or mediastinal masses
	R **L** ☐ ☐	☐ hilar elevation
	R **L** ☐ ☐	☐ mediastinal shift
	R **L** ☐ ☐	☐ tracheal or bronchial compression
	R **L** ☐ ☐	☐ unilateral air-trapping
	R **L** ☐ ☐	☐ lobar collapses
		☐ doughnut sign on lateral chest X-ray

Bilateral air trapping ☐ **Y** ☐ **N**

Cardiomegaly ☐ **Y** ☐ **N**

Normal Chest X-ray ☐ **Y** ☐ **N**

13.5 Appendix 5: Wits HREC Certificate for this Study

M140421

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140421

NAME: (Principal Investigator)	Dr Nasreen Mahomed
DEPARTMENT:	Radiology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Diagostic Utility of Chest X-Rays in Childhood Community Acquired Pneumoia in the Era of Molecular Diagnostics, Antiretroviral Therapy, Bacterial Conjugate Vaccines ad Computer Added Diagnosis
DATE CONSIDERED:	25/04/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof SA Madhi
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 03/06/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

16/7/2014

M140421Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

13.6 Appendix 6: Wits HREC for the PERCH Study, South African Site

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Professor Shabir A Madhi

CLEARANCE CERTIFICATE	**M10M101129**
PROJECT	The Pneumonia Etiology Research for Child Health Project (PERCH)
INVESTIGATORS	Professor Shabir A Madhi.
DEPARTMENT	Respiratory and Meningeal Pathogens Research Unit
DATE CONSIDERED	26/11/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 13/01/2011 **CHAIRPERSON** .....
pp (Professor PE Cleaton-Jones)

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

DECLARATION OF INVESTIGATOR(S)

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

13.7 Appendix 7: CHBAH MAC Permissions for the PERCH Study, South African Site

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 11 November 2010

TITLE OF PROJECT:

The pneumonia etiology research for child health project

UNIVERSITY:

Principal Investigator: Professor S Madhi

Department: Respiratory and Meningeal pathogens Research Unit

Supervisor (If relevant):.....

Permission Head Department (where research conducted) Yes (professor Pettifor)

Date of start of proposed study: Feb 2010

Date of completion of data collection: May 2013

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

PROF JOHN PETTIFOR
MBBCh, FCP (S.A.)
CHIEF PAEDIATRICIAN

Recommended

Approved/~~Not Approved~~

13.8 Appendix 8 Report from Turnitin

I, Nasreen Mahomed, declare that I understand the concept of plagiarism thorough the guidelines of the University of Witwatersrand, Johannesburg and denial of plagiarism in my research thesis. I have attached a plagiarism report from turnitin.

_____

Signature of Candidate

6 June 2017

Date