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Epidemiology of Childhood Pneumonia

in the Era of Antiretroviral Therapy and Bacterial **Conjugate** 163

Vaccines David Paul Moore Student Number: 9101069-G A Thesis

submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Doctor **of** Philosophy **in the branch of** Medicine **Johannesburg,** 2018 **Declaration I,** 103

David Paul Moore, hereby

declare that this Thesis is my own, unaided **work. It is being submitted for the Degree of Doctor of Philosophy** of Medicine **at the University of the Witwatersrand, Johannesburg. It has not been submitted** before **for any degree or examination at any other University.** 81

David Paul Moore 4th September 2018, in Johannesburg ii Epigraph '[. . .] microbiological evidence of infection must be considered in the context of several fundamental difficulties found in respiratory diagnostics, including [. . .] complexities in determining whether a detected pathogen has a causal role in the illness.' (Bhat N et al. 2012) 'Establishing the etiologic agent responsible for pneumonia [in children] is difficult.' (Schuchat A and Dowell SF. 2004) 'It is rarely possible to be certain of the cause of pneumonia in a child.' (Silverman M et al. 1977) 1 אטתא תְלֶהקּ 1 ו יַא לְכ דח דָם שׁ תחת שׁה אתשָׁמ '. . . and there is nothing new under the sun.' (Ecclesiastes 1:9) iii Dedication I dedicate this work to my wife, Miriam, in recognition of the love and encouragement which she has given me during the months of data analysis and preparation of this thesis; this, during our first three years of marriage.

I also dedicate this work to my children, Dov Ber **and** 866

Gila, in the hope that they will be as fascinated by the world as their father is, and be inspired to enquire, question and conduct research with as much enthusiasm as he does. iv Publications & Conference Presentations Arising from This Study Publications

Moore DP, Higdon MM, Hammitt LL, Prosperi C, DeLuca AN, Da Silva P 381

et al. The incremental value of repeat induced sputum and gastric aspirate samples for the diagnosis of pulmonary tuberculosis in young children with acute community-acquired pneumonia. Clin Infect Dis 2017;64 Suppl 3:S309-16. 6

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findings from the PERCH Study. Paediatric Research Day **2017,** 32

University of the Witwatersrand Faculty of Health Sciences, Johannesburg. 824

Oral Presentation: 01 December 2017. v Abstract Background

Pneumonia is the leading non-neonatal cause of under-5 death globally, and in South Africa. 644

Human immunodeficiency type 1 (HIV)- infection and -exposure are risk factors for pneumonia in 61

children. Aim We appraised the aetiology of under-5 pneumonia in the era of access to bacterial conjug- ate

vaccines targeting Haemophilus influenzae type b and Streptococcus pneumoniae 27

and well- functioning

prevention of mother-to-child transmission and antiretroviral treatment (ART) programmes to prevent and 80

treat paediatric HIV infection. Methods

This research was conducted within the framework of the 812

Pneumonia Etiology Research for Child Health (PERCH) study, at the South African PERCH site (Chris Hani Baragwanath Academic Hospital, Soweto, Gauteng Province). 2

Cases,

aged 1-59 months hospitalised with World Health Organization-defined severe or very severe pneumonia 65

(according to pre-2012 definitions) from mid-August 2011 through end-August 2013 were compared to age-frequency, HIV-status matched controls. The aetiologic fraction of pneumonia attributed to each potential pathogen was calculated through comparison of nasopharyngeal-oropharyngeal (NP/OP) swab and whole blood PCR results, using conditional logistic regression. vi Abstract vii Results Pneumonia incidence (per 100 000 children) was 1 755.00 (95% CI, 1 701.8 to 1 809.5) overall, highest in younger

children, HIV-infected and HIV -exposed, uninfected (HEU) children. 12

Respiratory viruses contributed 0.59 (95% CI, 0.47-0.62) of the 'fraction of association' (FA) with radiologically-confirmed pneumonia, whereas bacteria were associated with 0.29 (95% CI, 0.18-0.35) in the cohort. Respiratory viruses predominated in HEU (FA

0.53; 95% CI, 0. 39 -0. 58) and HIV- unexposed children (FA 0. 57; 95% CI, 0. 43 -0. 648

61). Opportunistic pathogens (human cytomegalovirus (CMV) and Pneumocystis jirovecii) were the predominant organisms

in HIV-infected children (FA 0. 58; 95% CI, 0. 38 -0. 558

65).

Respiratory syncytial virus (RSV) was **the most** important organism **associated with** 878

case-status in

HIV-uninfected children (FA **0.** 31; **95% CI, 0.** 30 **-0.** 960

32) and HIV-infected children on ART (FA 0.21; 95% CI, 0.16-0.21). CMV, P. jirovecii and Klebsiella spp. were identified as being the pathogens most frequently associated with death in children that underwent lung biopsy. Conclusion Strategies to shorten antibiotic therapy in HIV-uninfected children hospitalised with pneumonia may enhance antibiotic stewardship at the study site. Continued efforts at expediting initiation onto ART in HIV-infected children would likely impact favourably on the burden of opportunistic infection-associated pneumonia and its attendant mortality. Research into vaccination against RSV and CMV is a priority. Acknowledgements The support and guidance of the following individuals and/ or entities is greatly appreciated: To Professor Shabir Madhi for selecting me to participate in the South African contribution to

the Pneumonia Etiology Research for Child Health (PERCH) **project, and** 18

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based at the **Johns Hopkins Bloomberg School of Public Health** 1

– Professor Kate O' Brien, Professor Orin Levine, Dr

Maria Deloria-Knoll, Dr Danny **Feikin,** Ms **Andrea DeLuca,** Ms **Amanda Driscoll,** 832

Ms Meredith Haddix, Ms Melissa Higdon, Mr Daniel Park, Ms Christine Prosperi – for their support and encouragement throughout study conduct, data cleaning,

analysis and the **write-up** phases **of the** PERCH **project;** The assistance **of** 946

Mr Qiyuan Shi at

the International Vaccines **Access Center, Johns Hopkins Bloomberg School of Public Health,** 677

in sharing his R code for the logistic regression adjustment for multiple pathogens is greatly appreciated; To my colleagues at the Respiratory & Meningeal Pathogens Research Unit, some of whom participated actively in the set-up and smooth running of the PERCH study at the South African site, and all of whom encouraged me during the PERCH enrolment phase: Dr Peter Adrian, Dr Vicky Baillie, Dr Clare Cutland, Professor Ziyaad Dangor, Dr Michelle Groome, Dr Alane Izu, Dr Gaurav Kwatra, Ms Mari¨ette Middel, Professor Marta Nunes, Dr Susan Nzenze; To the dedicated team of women who, despite a rapid and frequent staff turn-over, assisted in all aspects of the PERCH project at the South African site, from study coordination, handling of logistics, participant enrolment, data collection, community visits for control recruitment viii Acknowledgementsix interviews and case follow-up activities, maintenance and updating of data, and data archiving and retrieval: Study coordinator – Sr Azwifarwi Mudau; Nursing staff – Sr Debra Katisi, Sr Audrey Kubheka, Sr Magare Lelaka, Sr Tsekabe Makgoba, Sr Matshediso Moilwa, Sr Malebo Motiane, Sr Sibonsile Moya, Sr Thondani Netshishivhe, Sr Minah Nkuna, Sr Mmabatho Selela, Sr Ndulela Titi, Sr Nonhlanhla Tsholetsane; Study Assistant – Ms Lerato Mapetla; Research Assistants – Ms Simphiwe Gasa, Ms Gudani Singo; Field Workers – Ms Cece Mgenge, Ms Nombulelo Monedi and Ms Nozipho Mthunzi; To the staff at the

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412 Nomenclature AC airways consolidation ABAU Acinetobacter baumannii ACINE Acinetobacter spp. ADENO adenovirus AF attributable fraction AFB acid-alcohol fast bacilli AIDS acquired immunodeficiency

population attributable fraction ARI

AIDS and Demographic Model 2008 BC blood culture BCG bacillus Calmette-Gu´erin BOSTID

CALB Candida albicans

CFRE Citrobacter freundii CHBAH

CI confidence interval CMV human cytomegalovirus Compl.complications Contam.contaminated CoNScoagulase negative staphylococcus COR229coronavirus 229E xxiv COR43coronavirus OC43 COR63coronavirus NL63 CORHKU coronavirus HKU1 CPARA Candida parapsilosis CPNEU Chamydophila pneumoniae CRF case report form CRPC-reactive protein Ct cycle threshold CXR chest radiograph CXR+ radiologically-confirmed pneumonia DHSDemographic Health Survey DTP

diphtheria, tetanus toxoid and pertussis vaccine 241

DTP

-Hib diphtheria, tetanus, pertussis, Haemophilus influenzae type b vaccine DTP/ Polio **diphtheria, tetanus** toxoid and **pertussis vaccine,** 129

and oral polio vaccine DTP3

third dose of diphtheria, tetanus toxoid and **pertussis vaccine** DTaP-IPV//HibCV **diphtheria, tetanus toxoid,** acellular **pertussis,** 639

inactivated polio with Haemo- philus influenzae type b conjugate vaccine ECLO Enterobacter cloacae ECOL Escherichia coli EFAE Enterococcus faecalis ELISA enzyme-linked immunosorbent assay EPI

Expanded Programme on Immunisation EPI-SA South African Expanded Programme on Immunisation 668

EPIC Epidemiology of Pneumonia in the Community ESBLextended spectrum β-lactamase ETT endotracheal tube EV enterovirus FA ‘fraction of association’ FLU influenza virus

FLUA influenza A virus FLUB influenza B virus FLUC influenza C virus 45

FTDResp-33FastTrack Diagnostics Respiratory Pathogens 33 GA gastric aspirate GABRIEL

Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries GASGroup **A** 219

β-haemolytic streptococcus GEMSGlobal Enteric Multicenter Study GNR Gram-negative rods HBOV human bocavirus HBV hepatitis B vaccine HEU HIV-exposed, uninfected Hib [or

HIB] Haemophilus influenzae type b HibCV Haemophilus influenzae type b conjugate vaccine 318

HINF non-type b Haemophilus influenzae HINFL Haemophilus influenzae

HIV human immunodeficiency virus type 1 **HIV+ HIV-infected HIV- HIV-uninfected** 61

HIV/AIDShuman

immunodeficiency virus and acquired immunodeficiency syndrome 565
HIVVL **HIV** viral load HMPV **human**

metapneumovirus HREC Human Research Ethics Committee (Medical)

ICU intensive care unit IFA indirect fluorescent antibody 929

IMCI Integrated Management of Childhood Illness IPD invasive pneumococcal disease IQR interquartile range 616

IRR incidence rate ratio ISinduced sputum JhbJohannesburg KLEBS Klebsiella spp. KPNE Klebsiella pneumoniae LA lung aspirate LMCI lower middle income country log10decimal logarithm LPF low power field LRTI lower respiratory tract infection lytA pneumococcal autolysin gene MCAT Moraxella catarrhalis MCPP microbiologically-confirmed pneumococcal pneumonia MCV measles-containing vaccine MGIT Mycobacterial Growth Indicator Tube MPNEU Mycoplasma pneumoniae MRSA methicillin resistant Staphylococcus aureus MTA Materials Transfer Agreement MtbMycobacterium tuberculosis Negnegative NHLSNational Health Laboratory Service NP/OP nasopharyngeal-oropharyngeal Oppor.opportunistic pathogens OPV oral polio vaccine ORodds ratio PAER Pseudomonas aeruginosa PARA parainfluenza virus PARA1

parainfluenza virus 1 PARA2 **parainfluenza virus 2** PARA3 **parainfluenza virus 3** PARA4 **parainfluenza virus 4** **33**

PASPeriodic Acid-Schiff PCRpolymerase

chain reaction PCV pneumococcal conjugate vaccine PCV7 7 **-valent pneumococcal conjugate vaccine** PCV9 9 **-valent pneumococcal conjugate vaccine PCV13** 13 **-valent pneumococcal conjugate vaccine** **153**

PEPFAR United States President's Emergency Plan for AIDS Relief **714**

PERCH Pneumonia Etiology Research for Child Health PF pleural fluid PJP Pneumocystis jirovecii P. jirovecii pneumonia PLANS Pneumonia Lung Autopsy Needle Study PNEU Streptococcus pneumoniae

PMTCT prevention of mother-to-child transmission [of HIV] **3**

Pos positive PPD purified protein derivative PSEUPseudomonas spp. PTB pulmonary tuberculosis PV/EVparechovirus/ enterovirus RAD reactive airways disease RCT randomised controlled trial RHINO human rhinovirus RMPRU Respiratory & Meningeal Pathogens Research Unit ROCreceiver operating characteristic RR relative risk RSVrespiratory syncytial virus RTHC Road-to-Health Card RTI respiratory tract infection RV rotavirus vaccine SASouth Africa SARI Severe Acute Respiratory Illness SASPSalmonella spp. SAURStaphylococcus aureus SCERSaccharomyces cerevisiae SDstandard deviation STGGskim milk-tryptone-glucose-glycerol [medium] TB tuberculosis Td tetanus toxoid, low-dose diphtheria vaccine TU tuberculin units

UNICEF United Nations Children's Fund WAZ weight-for-age Z-score **67**

WB whole blood WHO World Health Organization Preface This thesis is presented in the 'block' format, presenting an Introduction (which includes the literature review which sets the context of the research), Methodology Chapter, six Results Chapters, a Discussion Chapter and a brief Concluding Chapter. The afore-mentioned ten Chapters are followed by the References. Chapters 1 through 10, and the References form the body of the thesis and may be read in isolation of the ensuing Appendices. The Appendices, which follow after the References, contain supporting, supplementary materials which underpin analyses contained within the body of the thesis. By word of caution, the Appendices are extensive but are included for convenience should the examiner (or interested other reader) feel the need to review the raw materials from which the main body of the thesis is derived. The PDF version of this thesis contains hyperlinks – highlighted in blue font – which may assist in navigating this document. xxx xxxi Colophon This document was typeset in pdfLATEX, using MiKTEX version 2.9 and TEXworks. The document class is {thesis} and the font style is Latin Modern Roman, 11pt for the main body of the text. The following LATEX packages were used to build this document: nu bie h ve ac h , re x, o , tn Bibliographic data were stored in BIBTEX format and processed using BibLATEX. Where mentioned in table footnotes, tables were derived using the stargazer package in R. 1 Introduction 1.1The Global Burden of Under-5 Pneumonia It is estimated that

120.4 million episodes of pneumonia, **14.1 million of** which were **severe** pneumonia episodes, occurred **in children** **15**

<5 years of age globally in 2010 and that 1.3 million under-5 pneumonia-related deaths occurred in 2011 [1]. The majority (83.8 million; 69.6%) of these under-5 pneumonia episodes occurred in

the World Health Organization (WHO) African and South-East Asian **regions** **964**

[1], concentrated mostly in sub-Saharan Africa [2, 3]. In 2008, 2010, and 2013 respectively, pneumonia caused 1.2 million, 1.1 million and 800 000 deaths (i.e., 13% to 14% of

deaths) in the one- **to 59-month age group** 918

[2, 4, 5]. Mortality rates due to pneumonia in the one- to 59-month age group had declined by 35% globally between 2000 and 2012 [6], and by 73% since the early 1990s [6, 7]; however, annual rates of decline were significantly slower in Africa (-1.8%, Uncertainty Range -2.3% to -1.2%) than in South-East Asia (-4.7%, Uncertainty Range -5.2% to -4.3%) [2]. Well into the second decade of the 21st Century, under-5 pneumonia deaths remain preventable through poverty alleviation [8–10] and health systems strengthening [11, 12], including intensification of immunisation activities [3, 13–19]. Globally, although diarrhoeal illness contributes a 14-fold higher absolute

burden of disease in the under-5 **age group** compared **to** 402

pneumonia (1.7 billion versus 120.4 million disease episodes, respectively), pneumonia contributes to almost twice the number of under-5 deaths (1.3 million) than does diarrhoea (0.7 million) [1]. 1.2World Health Organization (WHO) Definitions for Childhood

Pneumonia Pneumonia is an inflammatory condition **of the lungs, usually** precipitated **by** 429

infectious agents (respiratory viral, bacterial or fungal), and very occasionally by chemical insults, which culmin- ates in compromised alveolar function, leading to hypoxaemia [20]. In the most severe forms of pneumonia, an extreme barrier to alveolar gas exchange occurs, resulting in hypercapnia, respiratory acidosis and respiratory collapse [20–22]. Childhood pneumonia is a difficult disease process to diagnose and define in the clinical context, and has been classified in broad terms by 1 1. Introduction 2 WHO so that young

children presenting to health facilities **with symptoms and signs** suggestive **of** 908

pneumonia are prioritised for referral to higher-level facilities if criteria for escalation of care are present [7, 23–26]. World Health Organization definitions for child pneumonia are based on observational studies which were conducted in West and Southern Africa, South-East Asia and Papua New Guinea in the 1980s [27]. Until recently, WHO endorsed a four-tiered classification of childhood pneumonia which comprised of:

‘no pneumonia, cough or cold’, ‘pneumonia’, ‘severe pneumonia’ 524

and ‘very severe pneumonia’ (Table 1.1), recommending

that children with ‘severe’ or ‘very severe’ **pneumonia be** admitted **to hospital for** 808

antibiotic and supplemental oxygen therapy whilst those with ‘no pneumonia: cough or cold’ or ‘pneumonia’ could safely be managed in the ambulatory setting with follow-up at primary care clinics in two to five days if symptoms fail to resolve [23]. A revised pneumonia classification system, which comprises three clinical entities –

‘no pneumonia, cough or cold’, ‘pneumonia’ and ‘severe pneumonia’ 524

– was proposed by WHO in 2012 (Table 1.2) [26, 28, 29]. According to the revised WHO pneumonia classification system, children previously labeled as having

‘severe pneumonia’ may **be managed at home with oral antibiotics** 533

if room air saturations are >90%, with a recommendation for clinical review within three days if not responding to therapy [26]. The WHO classification of childhood pneumonia is highly sensitive but lacks specificity [30, 31]. Consequently, children with other life-threatening conditions may be misclassified as having pneumonia through the use of this classification system [27, 32–36]. Classification systems that throw the net broadly in order to detect children

at high risk of severe pneumonia-associated **morbidity and mortality** are particularly relevant **in** 839

light of the considerably higher case fatality ratio (CFR) observed amongst under-5 pneumonia cases compared to diarrhoea cases. Using a simplistic approach which assumes that pneumonia and diarrhoea do not occur concurrently, the odds of dying among paediatric pneumonia cases are 27-fold (95% confidence interval (CI), 26.91 to 27.06) greater compared to diarrhoea cases (derived from [1]). Only 59% of young children with the symptoms of 'cough and difficulty breathing' – the key indicator symptoms of childhood respiratory illness according to the WHO pneumonia case definition – worldwide, and 46% in sub-Saharan Africa, were taken for evaluation at health care facilities by their care givers in 2012 [37], with considerable variation in health seeking behaviours (ranging from 27% to 79% of children with pneumonia being evaluated at health care facilities) between countries [38]. Tab. 1.1: WHO Classification of Severity of Respiratory Infections in Young Children: 2005 Definitions [23] ClassificationCriteria Recommended Management No Pneumonia, cough or coldCough or difficulty breathing with

no signs of pneumonia, **severe pneumonia or very severe pneumonia** PneumoniaCough **or** difficulty **breathing** 426

with fast breathinga and/ or definite crackles on auscultation Severe PneumoniaCough

or difficulty breathing with lower chest wall indrawing 15

Home care; soothe the throat and relieve cough with safe remedy; advise the mother when to return; follow up in five **days if not improving; if coughing for** 51

>30 days, follow up chronic cough instructions

Home care; give appropriate antibiotic for five **days; soothe the throat and relieve cough with a safe remedy; advise the mother when to return immediately; follow up in** two **days** Admit to hospital; **give** 145

recommended antibiotic; manage the airway; treat high fever if present Very **Severe** 51

PneumoniaCough or difficulty breathing with

central cyanosis/ severe respiratory distressb / **not able to drink Admit to hospital; give** recommended antibiotic; **give oxygen; manage the airway; treat high fever if present** 440

1. Introduction 3 a

Fast breathing: ≥60 breaths/ min **in a child aged <2 months; ≥50 breaths/** min **in a child aged 2-11 months; ≥40 breaths/** min **in a child aged 1-5 years;** 106

b Severe respiratory distress: head nodding. WHO = World Health Organization. Tab. 1.2: WHO Classification of Severity of Respiratory Infections in Young Children: 2012 Definitions [26] ClassificationCriteria Recommended Management No Pneumonia, cough or coldCough or difficulty breathing with

no signs of pneumonia, **severe pneumonia or very severe pneumonia** PneumoniaCough **or** difficulty **breathing** 426

with fast breathinga / lower chest wall indrawing

Home care; soothe the throat and relieve cough with safe remedy; advise the mother when to return; follow up in five **days if not improving; if coughing for** 51

>14 days, refer to chronic cough algorithm

Home care; give appropriate antibiotic; advise the mother when to return immediately; 641

follow up after three days Severe PneumoniaCough

or difficulty breathing with oxygen saturation <90%/ central cyanosis/ severe respiratory 688

distressb / signs of pneumonia with general danger signsc

Admit to hospital; give recommended antibiotic; give oxygen if saturation <90%; **manage the airway; treat high fever if present** 145

1. Introduction 4 a

Fast breathing: ≥60 breaths/ min **in a child aged <2 months; ≥50 breaths/** min **in a child aged 2-11 months; ≥40 breaths/** min **in a child aged 1-5 years;** 106

b

Severe respiratory distress: grunting/ very severe chest indrawing; 473

c

General danger signs: **inability to breastfeed/ drink; lethargy/ reduced level of consciousness; convulsions.** 473

WHO = World Health Organization. 1. Introduction 5 1.3Epidemiology of Childhood Pneumonia A synopsis of child pneumonia studies compiled by the WHO in 1993 [39] appraised the published literature from 1966 to 1990 – 55 studies in all – and reviewed clinical and epidemiological evidence up to the early 1990s. Recurring themes in the epidemiology of childhood pneumonia were that acute respiratory infections (ARIs) were common in young children who experienced between four and seven episodes of respiratory illness per year (up to 14 episodes of acute respiratory illness per child per year in Burkina-Faso), that the incidence of pneumonia decreased markedly after the first two years of life, that seasonal peaks (usually coinciding with the winter months) of respiratory illness was the norm, and that males tended to have a greater burden of illness than females (Table 1.3).

Risk factors for community-acquired pneumonia (CAP) **in children**<5 years **of** 15

age include prematurity, young age, immunosuppressive conditions including malnutrition and human immunodeficiency virus type 1 (HIV) infection, and environmental factors including overcrowding, inadequate housing,

indoor air pollution, passive **exposure to cigarette smoke and** 910

winter season [40–42]. 1.3.1Childhood Pneumonia in sub-Saharan Africa A swathe

of sub-Saharan African countries, **extending** contiguously **from** Mauritania **and** Mali **in West** Africa **to** 775

Mozambique in Southern Africa, had

under-5 mortality rates **in** excess of **80 per 1 000 live births in** 678

2010 through 2012 [43, 44],

with pneumonia being **the leading cause of childhood** death in **the** 6

region [2]. The combined estimate of under-5 mortality in sub-Saharan Africa in 2016 was 77 per 1 000 live births (90% Uncertainty Interval, 69 to 86

per 1 000 live births) [45], **slightly** lower **than the** 837

global under-5 mortality estimate of 85 **to** 91 **per 1 000 live births** 102

in 1990, and in stark contrast to the 2017 estimate of

under-5 mortality globally (38 **to** 48 **per 1 000 live births)** 768

[6, 37, 45–48]. Socioeconomic and political instability [49, 50], over-burdened and under-staffed health systems [51–54] and inefficient service delivery [55–57], coupled with HIV prevalence which, apart from predisposing those infected with HIV to opportunistic infections, disrupts household income security and contributes to the cycle of HIV-related poverty [58–65], contribute to the burden of

disease and mortality in sub-Saharan Africa. An illustration **of** the precarious **health** 368

systems infrastructure in Africa is that, although a quarter of the global disease burden (all diseases, combined) arises here,

only 3% of the world's healthcare **workers** reside in **the** 873

region [53]. 1. Introduction 6 Tab. 1.3: Epidemiologic Studies of Childhood Pneumonia 1969 to 1990 [39] Author Site Journal Year Published Main Findings Feldman India – Vellore Am J Epidemiol 1969 Highest illness incidence was in 6 to 11 month age group; seasonal peak. Kamath India – Vellore Am J Epidemiol 1969 Highest illness incidence was in 6 to 11 month age group; seasonal peak. Monto USA – Tecumseh, MI JAMA 1974 6.1 episodes of ARI in children <1 year; decreasing incidence of ARI with increasing age; boys had more ARI than girls. Oseasohn USA – Gallup, NM Am Rev Resp Dis 1978 Highest pneumonia incidence in <1 year olds; seasonal peak in ARI. Murphy USA – Chapel Hill, NC Am J Epidemiol 1981 Seasonal peak; maximum incidence of bronchiolitis in 6 to 11 month age group. Berman Colombia – Cali Pediatrics 1983 Frequency of ALRI decreased markedly after the first two years of life. Pio Literature review Proceedings of an 1984 Reductions in ARI mortality in developed countries, and hardly at all in International Workshop, developing; ARI in 30% to 60% children attending outpatient departments; ARI Sydney, August 1984 in 30% to 36% hospitalised children. Denny USA – Chapel Hill, NC J Pediatr 1986 Seasonal peak; maximum incidence of bronchiolitis in 6 to 11 month age group. Gratten Papua New Guinea – Goroka Biol Neonate 1986 HINFL and PNEU acquired within first 3 months of life – earlier for PNEU; longer carriage of PNEU. Lang Burkina-Faso – Bana Int J Epidemiol 1986 10 to 14 episodes of ARI per year. Leowski Literature review World Health Stat Q 1986 Estimated 4 million ARI-related deaths

in children <5 years annually (27% **of** all deaths **in this age group).** 154

Continued on next page . . . 1. Introduction 7 Tab. 1.3, continued from previous page . . . Author Site Journal Year Published Main Findings McConnochie USA – New York, NY Am J Pub Health 1988 7 to 12 month group had highest incidence of ARI overall; boys had more ARI than girls. Pickering Papua New Guinea – Tari Trans Roy Soc Trop Med 1988 Nasal carriage of PNEU 83% in children, 33% in mothers. Unlikely that PNEU Hyg transmission occurred from hands to respiratory tract. Spika Bangladesh – Teknaf area Ann Trop Med 1989

ALRI the single most important cause of death in the 729

1 to 59 month age group: highest death due to ALRI was in infants 1 to 5 months of age. Borrero Colombia – Cali Rev Infect Dis 1990 6.6 cases of ARI per child-year at risk, 1.7 cases of ALRI. Selwyn Multisite: 10 countries Rev Infect Dis 1990 ARI incidence highest in 6 to 11 month age group; wide variation in incidence rates due to different populations, climate/ geography, or syndrome classification methods. Tupasi Philippines – Manila Rev Infect Dis 1990 34/747 (4.6%) of ALRI episodes required hospitalisation. Decline in ARI incidence with increasing age. 6.1 episodes of ARI per child-year. Wafula Kenya – Nairobi Rev Infect Dis 1990 4.3 episodes of ARI per year – highest in infants.

ALRI = acute lower respiratory tract infection; ARI = acute respiratory infection; 730

HINFL = H. influenzae ; PNEU = S. pneumoniae ; Table produced using the stargazer package in R [66]. 1. Introduction 8 Young children, being among the most vulnerable members of society, are at particular risk of the ill-effects of inequities in health care provision [8, 67, 68]. The burden of pulmonary infectious disease in young children is impacted by socioeconomic, political and health indicators [18], and in 2010 the incidence of severe and very severe

acute lower respiratory infection (ALRI) in **children <5 years of age** was highest **in** 15

Africa, compared to other WHO regions (Figure 1.1) [69]. Over 3.0 million severe pneumonia episodes, and approximately 1.8 million

very severe pneumonia episodes, occurred **in children <5 years of age** 491

residing in the WHO Africa region in 2010, with a CFR of 3.9% (95% CI, 2.7% to 5.5%) in those hospitalised for pneumonia during that year [69]. Severe and very severe pneumonia (combined) in Africa – 4.8 million episodes in 2010 – represented one third of the developing world's under-5 pneumonia burden, with young children in the WHO Africa region contributing to two-thirds of the very severe under-5 pneumonia burden of the developing world (Figure 1.1) [69]. Case management of young children with pneumonia in Africa is impacted by patterns of caregiver health-seeking behaviour [70–74], limited access to health care [75–78], an over-burdened workforce of health care workers and intermittent interruptions in supply of essential drugs to health facilities which frequently translates into suboptimal clinical care [79–81]. Proximal and distal impediments to health care delivery in Africa have contributed to limited treatment coverage of children with pneumonia symptoms, with 28%, 30% and 39% of these children having received antibiotic therapy in 2008, 2011 and 2012 respectively [18, 37, 82]. 1.3.2Burden of Community Acquired Pneumonia in Hospitalised Children in sub-Saharan Africa: An Informal Meta-analysis I undertook a meta-analytic approach in interrogating

published data on the profile **of** paediatric hospital admissions **in sub-Saharan Africa,** 514

describing the burden and clinical course of children hospitalised with CAP from the mid-1950s until 2014. This search identified 448 108 paediatric hospitalisation episodes, at least 270 348 of which

occurred in children <5 years of age, 154

and spanning approximately 4 878.25 months (406.5 years) of observation (Figure 1.2 and Appendix A) [72, 73, 80, 83–251]. Using a random effects model to summarise proportions using the metafor package in R [252], indicated that pneumonia accounted for 27.7% (95% CI, 22.7% to 32.6%) of all paediatric 1. Introduction 9

Africa Americas E. Med. Europe S-E. Asia W. Pacific 731

Severe 22.6 19.8 12.1 7.3 17.8 17.3 V. Severe 15.0 3.0 · · · · · 3.7 6.3 CFR (%) 3.9 1.3 7.6 0.4 2.1 2.3

ALRI = acute lower respiratory infection CFR = case fatality ratio 15

E. Med. = Eastern Mediterranean S-E. Asia = South-East Asia V. Severe = very severeW. Pacific = Western Pacific Fig. 1.1: Incidence and Case-fatality Ratios of Childhood

Severe and Very Severe Acute Lower Respiratory Tract **Infection in the** 26

Six WHO Regions (2010) – Adapted from [69] 1. Introduction 10 admissions, and 32.3% (95% CI, 21.6% to 42.9%) in under-5s (Figure 1.3, Table A.9), with a mean CFR of 9.0% (95% CI, 8.1% to 9.9%) (Figure 1.4, Table A.10). Case fatality ratios were particularly high in

children admitted to the intensive care unit (ICU) **(mean** 52

34.7%; 95% CI, 27.8% to 41.5%), malnourished children (mean 32.6%; 95% CI, 19.8% to 45.4%), and those that were HIV-infected (mean 15.5%; 95% CI, 12.0% to 19.0%) (Figure 1.4). By contrast, the mean CFR in HIV-uninfected children with pneumonia was 2.3% (95% CI, 1.6% to 2.9%) (Figure 1.4). 1.4Pneumonia Aetiology Studies in Children Pneumonia aetiology studies in children are hampered by difficulties in sampling respiratory tract secretions in order to attribute which pathogens represent colonisers and which pathogens are causative of the disease process [93, 253, 254]. Young children cannot cooperate in producing expectorated sputum samples, and collection of induced sputum (IS) specimens, although safe and easy to perform in young children [255, 256], is not routinely undertaken other than for identification of Mycobacterium tuberculosis (Mtb) in children suspected of having pulmonary tuberculosis (PTB). The nasopharynx is heavily colonised with commensal organisms, including those frequently implicated in pneumonia aetiology, therefore sputum specimens may culture commensal organisms, not necessarily those causing a pneumonia episode [257, 258]. Blood cultures are useful in attributing bacterial aetiology in only a few cases, because prior antibiotic exposure, low blood inoculum volumes and delays in sample processing all hamper blood culture yields, in addition to which only a minority (ranging from 0.9% to 26.1%) of paediatric radiologically-confirmed pneumonia episodes are bacteraemic [119, 158, 253, 259–263].

The 'gold standard' method of sampling **for the** determination **of** pneumonia aetiology **is** 888

through lung aspiration; however, few centres outside of The Gambia have expertise in conducting this sampling methodology. This despite lung aspirates (LAs) being demonstrated to be safe in centres that regularly perform this sampling technique, including a transient complication rate of 1.6% and no deaths in 493 pneumonia cases who underwent this procedure [264]. Nevertheless, lung aspiration is often viewed as being too invasive, especially when performed on critically ill infants with pneumonia. Furthermore, lung aspiration is best suited in cases with peripherally-located lobar consolidation on chest radiograph which is only present in 19% to 52% of childhood pneumonia cases [171, 265, 266], including in 44% (493/1 116) pneumonia cases in a review of The Gambian studies which detailed the utility of the procedure over a 25-year period [264]. 1. Introduction 11 Country (Number of Studies) [72, 73, 80, 83–251] Total Months Total Children Under-5 Children Angola (n=3) 139 497 263 Botswana (n=2) 72 323 323 Cameroon (n=2) 312 860 733 Central African Republic (n=2) 12 1 035 1 035 Cote d'Ivoire (n=2) 20 4 635 · · · Ethiopia (n=3) 84 1 480 1 467 Ghana (n=1) 22 1 032 1 169 Kenya (n=20) 333 41 861 25 199 Malawi (n=5) 100.75 71 077 71 076 Mali (n=1) 12 1 644 · · · Mozambique (n=3) 130 13 740 13 740 Namibia (n=1) 12 60 60 Niger (n=2) 72 1 009 948 Nigeria (n=18) 663 10 434 7 294 Senegal (n=1) 3 114 114 Sierra Leone (n=2) 144 11 931 8 746 South Africa (n=63) 1 907 210 359 114 700 South Africa & Zambia (n=1) 32 523 523 Sudan (n=1) 8 144 · · · Tanzania (n=4) 61 33 394 5 670 The Gambia (n=16) 343 20 370 10 720 Uganda (n=6) 43.5 2 896 2 369 Zambia (n=6) 108 16 335 2 714 Zimbabwe (n=8) 245 2 355 1 485 All Studies Combined (n=172) 4 878.25 448 108 270 348 Table produced using the stargazer package in R [66]. Fig. 1.2: African Childhood Pneumonia Studies 1. Introduction 12 Fig. 1.3: Random Effects

Meta-analysis of Proportion of Paediatric **Hospitalisations associated with** 898

Childhood

Pneumonia in sub-Saharan Africa Studies grouped **in** the **'Hospital Mortality** 880

Profile' category were studies that interrogated hospitalised paediatric cohorts primarily for the purposes of describing case- fatality rates, but which provided the

total number of children hospitalised, including **the number of children with** 762

pneumonia. For study references, please refer to Table A.9. Study Type (n) CFR /95% CI} A. I lospilal Cohort, Studies (n 28) 9.7 I8.0, I 1.3] 13. Il ospi lal Cohor(Stud itos - nol 1 ualuourishcd (u - 2'1) 8.1 [6.5, 9.6] C.·I I ospi1 a I Cohort St uclif'><- nml nonrislw(I (n-2):32.(; IHJ.s. <15. 11 D. Combined St.udics- IliV-inf (:'(;led (n 29)1 5.5 112.0, 19.01 8. Co111biued SLudics- III V-uuiu fect.ed (u -28)•2.3 [1 .6, 2.9] I". Pneumon ia Cohort Stucl i >s (n -I :I)10.8 1 9.0, 12.71 C:. Pneun1onia Ae iology St.udies (11 52)7.3 1 6.4, 8.21 H. I('U

('ohort Siudi<1' (n = I O)= u 127.8.'11.5J •f. De·rSimonian-Laird Random Effects Model for Subgroup {n=99) 9.0 {8.1 , 9.9} 0.0 10.020.0 :10.0 40.050.0 Observed Outcome Fig. 1.4: Random Effects Meta-analysis of Case Fatality Ratio associated with Childhood Pneumonia in sub-Saharan Africa OFR =case fatality ratio; HIV =human immunodeficiency virus type 1; IOU =intensive care unit; For study references, please refer to Table A.IO. 1. Introduction 14 In 23 pneumonia aetiology studies that utilised lung aspiration for bacterial culture in the era before HibCV and PCV were introduced into national immunisation programmes, 49.9% of 1 973 LAs were culture-positive compared to 16.2% of blood cultures from the same children (Table 1.4). The most frequently isolated bacterial species on lung aspiration included Staphylococcus aureus (19.8%), Streptococcus pneumoniae (14.6%) and Haemophilus influenzae (7.9%) (Table 1.4) [39]. Amongst children not exposed to antibiotics prior to lung aspiration, S. pneumoniae was the most prevalent pathogen isolated (129/385; 33.5%) (Table 1.4). The complication rate of lung aspiration was 5.3% (Table 1.4) [39]. Pneumococcus

and H. influenzae were the most frequently isolated **bacteria in children** presenting **with** **491**

bacteraemic pneumonia [39]. Respiratory

viruses were detected in 29% **of** those tested, **and respiratory** syncytial **virus** **901**

(RSV) was the predominant virus isolated (74.1%), followed by human rhinovirus (25.0%), parainfluenza virus type 3 (10.0%), enterovirus (10.0%), adenovirus (7.6%) and influenza A (5.9%). Mixed bacterial-viral infections were observed in 9% of childhood pneumonia cases [39]. 1.4.1Studies which highlight the differences in the aetiology profiles of adult and child pneumonia The EPIC Study

in the United States [267, 268] In **the Epidemiology of** Pneumonia **in the** **803**

Community (EPIC) Study, Jain et al [267, 268] studied a series of adults and children with radiologically-confirmed pneumonia in the United States, using blood culture, sputum culture and nasopharyngeal-oropharyngeal (NP/OP) swab

polymerase chain reaction (PCR) to determine **the** profile **of pathogens** associated with adult **and** **550**

child pneumonia aetiology. Recruitment started in January 2010 and continued through June 2012. A convenience sample of asymptomatic community controls was enrolled for NP/OP swab PCR testing so as to enhance the accuracy of interpretation of the case NP/OP swab results. Pertinent results of these studies are summarised and compared in Table 1.5. Respiratory viruses were demonstrated to contribute a substantial proportion of paediatric pneu- monia episodes (73%, including 66% 'pure viral' and 7% 'mixed' viral and bacterial pneumonia episodes) compared to 27% amongst adults (which included 22% single-viral infections, 2% viral-viral co-infections and 3% with bacterial-viral mixed infections) [267, 268]. Of note in EPIC, was that a pathogen was attributed as being causative of pneumonia in 81% of children [268], whereas only 38% of adult pneumonia episodes had a defined aetiology [267]. 1. Introduction 15 Tab. 1.4: Lung Aspirate Studies of Childhood Pneumonia 1966 to 1988 [39] Author Site Journal Year Pub- lished LA Sample Size PNEU (n, %) HINFL (n, %) SAUR (n, %) Total Pos (n, %) Compl. (n, %) Pos BC (n, %) Schuster Chile – Santiago Pediatrica (Chile) 1966 125 26 (20.8) 19 (15.2) 15 (12.0) 67 (53.6) 2 (1.6) Sinha India – Calcutta Pediatr 1966 25 3 (12.0) 7 (28.0) 0 (0.0) 9 (36.0) 2 (8.0) Hughes India – Calcutta Pediatr 1969 18 2 (11.1) 6 (33.3) 0 (0.0) 6 (33.3) 1 (5.6) Klein USA – Pediatr 1969 28 4 (14.3) 0 (0.0) 9 (32.1) 15 (53.6) 4 (14.3) Mimica Boston, MA Chile – Santiago Am J Dis Child 1971 505 5 (1.0) 15 (3.0) 151 228 13 (2.6) (29.9) (45.1) Mimica Colombia – Am J Dis Child 1971 31 5 (16.1) 3 (9.7) 1 (3.2) 10 (32.3) 4 (12.9) 1 (3.2) Albornoz Medell´ın Colombia – Bogat´a Bol Med Hosp Infant 1973 123 2 (1.6) 1 (0.8) 16 (13.0) 27 (22.0) 4 (3.3) 32 (26.0) Alix Philippines – Cebu (Mex) Philippine J Pediatr 1973 68 2 (2.9) 3 (4.4) 54 (79.4) 60 (88.2) 3 (4.4) 5 (7.4) Continued on next page . . . 1. Introduction 16 Tab. 1.4, continued from previous page . . . Author Site Journal Year Pub- lished LA Sample Size PNEU (n, %) HINFL (n, %) SAUR (n, %) Total Pos (n, %) Compl. (n, %) Pos BC (n, %) Rozov Brazil – S˜ao Paulo Pediatr Prat 1974 37 15 (40.5) 3 (8.1) 1 (2.7) 20 (54.1) 9 (24.3) (S˜ao Paulo) Castro Costa Rica – Revista M´edical del 1975 100 19 (19.0) 1 (1.0) 15 (15.0) 39 (39.0) 8 (8.0) San Jos´e Hospital Nacional de Nin˜os Dr. Carlos S´aenz Herrera Rapkin USA – Newark, Clin Pediatr 1975 27 3 (11.1) 0 (0.0) 0 (0.0) 3 (11.1) 3 (11.1) 0 (0.0) New Jersey Escobar Colombia – Cali Pediatr 1976 102 5 (4.9) 4 (3.9) 8 (7.8) 19 (18.6) 16 (15.7) Silverman Nigeria – Zaria Arch Dis Child 1977 88 45 (51.1) 10 (11.4) 10 (11.4) 70 (79.5) 4 (4.5) 4 (11.0) Ferreira Brazil – Recife J Pediatr 1978 60 25 (41.7) 12 (20.0) 0 (0.0) 34 (56.7) 4 (6.7) (Rio de Janiero) Shakunthala India – Hyderabad Indian Pediatr 1978 60 14 (23.3) 0 (0.0) 14 (23.3) 31 (51.7) 3 (5.0) 6 (46.0) Cunanan Philippines – Philippine J Pediatr 1979 185 17 (9.2) 11 (5.9) 55 (29.7) 131 4 (2.2) 7 (3.8) Manila (70.8) Diallo Nigeria – Zaria Nigerian Med J 1979 56 10 (17.9) 0 (0.0) 8 (14.3) 39 (69.6) Diakparomre Nigeria – Nigerian Med J 1981 73 6 (8.2) 2 (2.7) 22 (30.1) 42 (57.5) 4 (5.5) Benin City Continued on next page . . . 1. Introduction 17 Tab. 1.4,

continued from previous page . . . Author Site Journal Year Pub- lished LA Sample Size PNEU (n, %) HINFL (n, %) SAUR (n, %) Total Pos (n, %) Compl. (n, %) Pos BC (n, %) Kaira India – Pune Indian Pediatr 1981 70 18 (25.7) 2 (2.9) 5 (7.1) 36 (51.4) 3 (4.3) Riley Papua New Guinea – Pediatr Res 1983 18 7 (38.9) 1 (5.6) 0 (0.0) 8 (44.4) Goroka Shann Papua New Guinea – Lancet 1984 83 24 (28.9) 32 (38.6) 2 (2.4) 48 (57.8) 7 (8.4) 31 (37.3) Goroka Wall Gambia – Fajara Bull World Health 1986 51 26 (51.0) 21 (41.2) 1 (2.0) 29 (56.9) 0 (0.0) 14 (27.5) Organ Ikeogu Zimbabwe – Arch Dis Child 1988 40 6 (15.0) 2 (5.0) 3 (7.5) 13 (32.5) 2 (5.0) Bulawayo Rozov Brazil – S˜ao Paulo Pediatr Prat 1974 37 15 (40.5) 3 (8.1) 1 (2.7) 20 (54.1) 9 (24.3) (S˜ao Paulo) Escobar Colombia – Cali Pediatr 1976 71 4 (5.6) 4 (5.6) 5 (7.0) 15 (21.1) 16 (22.5) Silverman Nigeria – Zaria Arch Dis Child 1977 88 45 (51.1) 10 (11.4) 10 (11.4) 70 (79.5) 4 (4.5) 4 (11.0) Ferreira Brazil – Recife J Pediatr 1978 60 25 (41.7) 12 (20.0) 0 (0.0) 34 (56.7) 4 (6.7) (Rio de Janiero) Riley Papua New Guinea – Pediatr Res 1983 18 7 (38.9) 1 (5.6) 0 (0.0) 8 (44.4) Goroka Shann Papua New Guinea – Lancet 1984 71 27 (38.0) 41 (57.7) 1 (1.4) 48 (67.6) 7 (9.9) 31 (37.3) Goroka Continued on next page . . . 1. Introduction 18 Tab. 1.4, continued from previous page . . . Author Site Journal Year Pub- lished LA Sample Size PNEU (n, %) HINFL (n, %) SAUR (n, %) Total Pos (n, %) Compl. (n, %) Pos BC (n, %) Ikeogu Zimbabwe – Bulawayo Arch Dis Child 1988 40 6 (15.0) 2 (5.0) 3 (7.5) 13 (32.5) 2 (5.0) Totala 289/1 973 155/1 973 390/1 973 984/1 973 100/1 899 100/617 (14.6) (7.9) (19.8) (49.9) (5.3) (16.2) Totalb 129/385 73/385 20/385 208/385 42/367 35/119 (33.5) (19.0) (5.2) (54.0) (11.4) (29.4) a Total in all children with lung aspirates obtained; b Total in children with lung aspirates done before they were exposed to antibiotics; BC = blood culture; Compl. = complications; HINFL = H. influenzae ; LA = lung aspirate; PNEU = S. pneumoniae ; Pos = positive; SAUR = S. aureus ; Highlighted rows indicate lung aspirates collected before antibiotics were administered to study participants; Table produced using the stargazer package in R [66]. The SARI Programme in South Africa [242, 269] During the course of the

Severe Acute Respiratory Illness (SARI) Programme undertaken **in South Africa** between **February 2009** and **December** **169**

2012, Cohen et al [242, 269] studied the aetiology of severe acute respiratory illness

in a large, prospective **cohort of adult** and paediatric **patients,** hospitalised at **five** **59**

public sector hospitals in four of South Africa's nine provinces. Severe acute respiratory illness was defined as an illness precipitating hospitalisation of less than seven days' duration, associated with acute

onset of fever >38 ◦C, cough or sore throat, and shortness of breath or difficulty breathing and **3**

did not require radiologic confirmation of pneumonia for inclusion into the study. Nasopharyngeal aspirates and whole blood were collected for multiplex PCR for respiratory viruses and pneumococcal autolysin gene (lytA) PCR testing, respectively. No control group was enrolled into these studies. The prevalence of respiratory viral

infection in the **children <5 years of age** **971**

was 78% overall [242], and 32% amongst those older than five years (extending through adult age groups, including those ≥65 years of age) [269]. Pathogen prevalence described in SARI are re-analysed in Table 1.5, so as to include all 'paediatric age group' participants (<15 years of age) into a single category for comparison against the 'adult' age groups. Similar as to what was described by Jain et al (page 14), the odds of SARI being associated with respiratory viral pathogens were almost uniformly greater in children compared to adults, with the only exception being illness attributable to influenza virus. The odds of viral-viral co-infections was 8-fold (95% CI, 7.14 to 8.98) greater in the paediatric age group, compared to adults; P<0.001. The odds of pneumococcal-associated severe acute respiratory illness was significantly greater in adult patients, however (Table 1.5). The importance of viral pathogenesis in paediatric respiratory infection

In the studies by Jain **et al** [267, 268] **and** Cohen **et al** **402**

[242, 269], RSV, human rhinovirus, human metapneumovirus (HMPV), parainfluenza virus, coronavirus and enterovirus infections were more prevalent in childhood pneumonia cases compared to adults (Table 1.5). Crucial to the understanding of the role of respiratory

viruses in the epidemiology **of childhood pneumonia,** is **the** need to appraise **prevalence of** detection **in** **511**

cases against that of a suitably-selected control Tab. 1.5: Comparison of the Aetiology Profiles of Childhood and Adult

Severe Acute Respiratory Illness Requiring **Hospitalisation in South Africa** 149

– Studies by Jain et al [267, 268] and Cohen et al [242, 269] EPIC [267, 268]SARI [242, 269] Pathogen Childrena (n=2 222; %) Adults (n=2 259; %)

OR (95% CI) P- valueb Childrenc **(n/N;** %) Adults **(n/N; %) OR (95% CI) P-** 81

valueb ADENO 248 (11.2) 32 (1.4) 8.74 (6.00 to 13.12) <0.001 2 176/8 288 (26.3) 499/5 964 (8.4) 3.90 (3.51 to 4.33) <0.001 COR 110 (5.0) 53 (2.3) 2.16 (1.54 to 3.01) <0.001 . . . . . EV . . . . . 920/8 943 (10.3) 76/6 502 (1.2) 9.70 (7.66 to 12.28) <0.001 FLU 149 (6.7) 132 (5.8) 1.16 (0.90 to 1.49) 0.234 677/8 954 (7.6) 557/6 507 (8.6) 0.87 (0.78 to 0.98) 0.024 HMPV 285 (12.8) 88 (3.9) 3.63 (2.82 to 4.70) <0.001 517/8 943 (5.8) 111/6 502 (1.7) 3.53 (2.87 to 4.35) <0.001 MPNEU 178 (8.0) 43 (1.9) 4.49 (3.18 to 6.45) <0.001 . . . . . PARA 151 (6.8) 67 (3.0) 2.38 (1.77 to 3.25) <0.001 830/8 943 (9.3) 180/6 502 (2.8) 3.59 (3.05 to 4.24) <0.001 PNEU 79 (3.6) 115 (5.1) 0.69 (0.51 to 0.93) 0.012 277/6 993 (4.0) 576/6 138 (9.4) 0.40 (0.34 to 0.46) <0.001 RHINO 606 (27.3) 194 (8.6) 3.99 (3.34 to 4.77) <0.001 3 304/8 943 (36.9) 1 078/6 502 (16.6) 2.95 (2.73 to 3.19) <0.001 RSV 622 (28.0) 68 (3.0) 12.53 (9.65 to 16.46) <0.001 2 252/8 943 (25.2) 285/6 502 (4.4) 7.34 (6.46 to 8.34) <0.001 >1 virus . . . . . 2 868/8 943 (32.1) 362/6 502 (5.6) 8.01 (7.14 to 8.98) <0.001 Other 81 (3.6) 174 (7.7) 0.45 (0.34 to 0.60) <0.001 . . . . . Detected 1 802 (81.1) 853 (37.8) 7.01 (6.16 to 8.12) <0.001 . . . . . a Children were defined as participants <18 years of age; b P-value comparing the prevalence of each pathogen in paediatric cases to the prevalence in adult cases of hospitalised severe acute respiratory illness ($\chi 2$ test); c Children were defined as participants <15 years of age; ADENO = adenovirus; CI = confidence interval; COR = coronavirus; Detected = any pathogen detected; EV = enterovirus; FLU = influenza viruses; HMPV = human metapneumovirus; MPNEU = M. pneumoniae ; OR = odds ratio; PARA = parainfluenza virus; PNEU = S.

pneumoniae ; RHINO = human rhinovirus; RSV = respiratory syncytial virus; 32

Table produced using the stargazer package in R [66]. 20 group which would allow for adjustment of hospitalised case pathogen detection against the background 'community-level' prevalence of that pathogen [270–273]. In other childhood pneumonia aetiology studies, respiratory viruses have been associated with hospitalisation, with the youngest children having the greatest burden of respiratory virus- associated pneumonia [274–279]. In Finland and Spain, 62% and 67% of radiologically-confirmed community-acquired pneumonia cases, respectively, were associated with respiratory viral patho- gens which were more prevalent in children <2 years of age [274, 276]. Studies of paediatric CAP in China implicate respiratory viruses in 32% to 58% of hospitalised patients [277–279], with the highest burden of respiratory viral-associated illness occurring in children <3 years of age [277, 279]. Eighty-one percent of under-5 children with radiologically-confirmed pneumonia in Sweden tested positive for respiratory viruses, compared to 56% of age- and season-matched controls with influenza virus, HMPV and RSV being strongly associated with case status [280]. A review of viral pneumonia highlighted that viral-associated CAP occurs consistently more frequently in children (49%; Range 43% to 67%) than adult (22%) pneumonia episodes [272]. Respiratory viral pathogens

may play a more prominent **role in the pathogenesis of** paediatric **pneumonia** – and particularly **in** 11

ex-premature infants, and

infants between the ages of 6 and 12 **months in** 810

whom maternal-derived passive immunity against common respiratory viruses would be suboptimal or waning – because infants lack ability to develop a durable and neutralising humoral response to viral surface glycoproteins, and tend to produce anti-viral antibodies with poor avidity [281]. Viral respiratory pathogens are poorly immunogenic regardless of age group, but repeated exposure to these pathogens tends to engender an antibody response protective against severe disease and which more effectively confines the infection to the upper respiratory tract [281]. A prevailing theory is that viral infections of the respiratory tract evoke inflammatory and immunologic effects which perturb the nasopharyngeal biome, leading to bacterial overgrowth which predisposes to bacterial (and mixed bacterial-viral) pneumonia [272, 282]. 1.4.2 Metanalyses of the

Burden of Disease Caused by Pneumococcus, **Haemophilus influenzae type b and** 707

Respiratory Syncytial Virus in Young Children 204

Three meta-analyses, interrogating the global burden of under-5 pneumonia caused by each of pneumococcus, H. influenzae type b (Hib) and RSV [283–285], highlight the numbers of children estimated to have suffered from pneumonia caused by these pathogens in the first decade of the 21st Century, and a fourth study [286] updates the RSV burden estimates in the era of established access to

H. influenzae type b conjugate vaccine (HibCV) **and pneumococcal conjugate** vaccine **(PCV).** Pneumococcus, **the** 120

leading cause of bacterial pneumonia in children globally, **is** 948

estimated to have caused

13.8 million episodes of childhood **pneumonia** and **741 000** pneumonia **deaths** 15

in the year 2000, with 406 000 (54.8%) of the under-5 pneumonia deaths occurring in Africa [283]. In 2000, Hib was implicated as a cause of under-5 pneumonia in 7.9 million children and as the pathogen causative of under-5 pneumonia death in 292 000 children globally, 146 000 (50.0%) of whom resided in the WHO African Region [284].

Estimates of the global burden of disease attributed to pneumococcus **and** Hib in **the** era **of** 388

access to bacterial conjugate vaccines were published in July 2018 [287], and indicate that the burden of pneumococcal and Hib pneumonia has declined by 37% and 88%, respectively, since 2000 [284, 287]. These reductions in disease burden were contemporaneous with up-scaled coverage of HibCV and PCV across the globe [287]. Nair et al [285] estimated that 33.8 million cases of under-5 RSV-related lower respiratory tract infections (LRTIs) occurred globally, at least 3.4

million of which **were severe enough to warrant hospitalisation** 15

in 2005, and that between 66 000 and 199 000 under-5 deaths occurred as a result of RSV pneumonia during that year. In 2015, RSV caused 33.1 million

acute lower respiratory tract illness events in **children <5 years of age,** 15

leading to 3.2 million hospitalisations and 59 600 deaths with almost half of the hospital admissions (1.4 million) and deaths (27 300) occurring

in children <6 months of age 470

[286]. These burden of disease meta-analyses illustrate that RSV

is the leading cause of under-5 LRTI **globally,** 506

and that strategies, including the development of vaccines, aimed at preventing disease caused by pneumococcus, Hib and RSV would have impact in decreasing the burden of disease in children under-5 globally. 1.4.3Multinational Studies of Childhood Pneumonia Aetiology in Resource Limited Settings: BOSTID, GABRIEL and PERCH Three multinational studies of

childhood pneumonia aetiology **in developing countries have been conducted** 500

to date [30, 288, 289]. The first of these, the Board on

Science and Technology for International Development (BOSTID) study, was conducted in the mid-to-late 1980s 245

[288].

The Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL) 49

study [289] and

the Pneumonia Etiology Research for Child Health (PERCH) study 2

[30] were conducted almost concurrently between 2010 and 2014, but targeted childhood populations in very different settings of access to bacterial conjugate vaccines and HIV prevalence (Figure 1.5). Essentially, BOSTID offered a 'snap shot' of childhood pneumonia in developing countries prior to access to HibCV and PCV and in an era before HIV-associated pneumonia was seen to be a major public health problem. GABRIEL and PERCH, however, were both conducted in the era subsequent to WHO recommendations for widespread use of HibCV and PCV in national immunisation programmes, and in the era of HIV. BOSTID The BOSTID study, which commenced in 1984 and was completed in 1988, was the first multi- national collaborative study aimed at interrogating

childhood pneumonia aetiology in low middle income countries (LMICs) and 34

stood out as the only prospective multi-national study which contributed to informing international policy with regards pneumonia case management in young children through the 1990s and 2000s [39, 288, 290]. Although difficulties have been observed with regards methodologies adopted in BOSTID, notably regarding

the lack of standardisation of a pneumonia case definition across the participating sites 225

[291], important insights into under-5 pneumonia aetiology in developing world settings was achieved through the study. BOSTID enrolled

children <5 years of age attending outpatient facilities and 421

hospitalised with

upper and lower respiratory tract infections 421

at twelve sites, situated in Africa (Kenya and Nigeria), the Americas (Argentina, Brazil, Colombia, Guatemala, Uruguay), the Eastern Mediterranean Region (Pakistan),

South-East Asia (Bangladesh and Thailand) and the Western Pacific Region 835

(Papua New Guinea and the Philippines) and was ambitious in 973

its scope in terms of geographic coverage, sample size and disease spectrum sampled. No control group was enrolled into BOSTID, -- • '<),_ I ·· S{, rly 0 BOS'i'JO 0 GABRII>L 0 PEHCII o fl0S1'm ,.._, vr·.HC'll 0 C:ABllffiL-": PERCH . .S..,_' •,...., '.:-.0 0.... t:: 1!, g· ? Fig. 1.5: Countries Participating in International Multi-site Studies of Child Pneumonia Aetiology in the Developing World Insert maps: Haiti and The Gambia. which limited the interpretation of aetiology attributions in the study; however, amongst children with LRTI, viruses (detected through cell culture and antigen immunofluorescence) [290] were observed in 14% to 64% of cases, with RSV being the leading viral agent in all sites [288]. Bacteria, detected through culture of blood or pleural fluid (PF) and/ or antigenuria [290], were attributed as a cause of LRTI in 5% to 40%

of cases and S. **pneumoniae and** H. **influenzae were the predominant** 195

bacterial pathogens [288]. GABRIEL The GABRIEL network case-control study of childhood pneumonia aetiology was conducted at nine centres in eight countries from 2010 to 2014 [289, 292]. Study sites were located in Africa (Madagascar and Mali), the Americas (Haiti and Paraguay),

South-East Asia (Cambodia **and two** centres **in** India) and **the Western Pacific** 780

Region (China and Mongolia). Cases were

children between two and 59 months of age hospitalised **with** radiologically-confirmed **pneumonia,** 702

and controls were children attending outpatient departments, or hospitalised for elective surgical procedures and had no features of respiratory illness. Cases and controls were age-frequency matched for pooled case-control analysis and adjusted population attributable fractions (aPAFs) of pneumonia caused by 19 viruses and five bacteria (identified through multiplex PCR of nasopharyngeal samples) were reported [289]. Overall, there were 1 758 participants including 888 (50.5%) cases. Importantly, there was a low HIV seroprevalence rate amongst study participants (19 of 1 577 tested; 1.2%) and low coverage with PCV (72 of 1 198 with available vaccination data; 6.0%). Pneumococcus (aPAF 42.2%; 95% CI, 35.5% to 48.2%), RSV (aPAF 18.2%; 95% CI, 17.4% to 19.0%), human rhinovirus (aPAF 11.2%; 95% CI, 7.5% to 14.7%), HMPV (aPAF 7.8%; 95% CI, 7.2% to 8.3%) and influenza virus A (aPAF 6.5%; 95% CI, 6.4% to 6.7%) were the top five pathogens associated with childhood pneumonia in the study overall, with pneumococcus being the most important organism in six of the nine study centres, RSV predominating in two centres (Cambodia and China), and human rhinovirus predominating at one of the Indian sites [289]. RSV and HMPV were the only organisms which were independently associated with hypoxic pneumonia in the GABRIEL study, but pneumococcus detected on PCR of whole blood was associated with in-hospital mortality [292]. PERCH The

PERCH study was a rigorously standardised **case-control study of** under-5 **pneumonia** con- ducted **in** 274

seven developing countries, including five sub-Saharan African

countries (The Gambia, Kenya, Mali, South Africa and **Zambia) and** 225

two countries in South-East Asia (Bangladesh and Thailand) [293]. PERCH cases included children

between the ages of one **and 59 months** hospitalised **with** WHO-defined **severe or very severe pneumonia** 72

and were compared to age-frequency matched, HIV-status matched controls to establish the aetiology of pneumonia at the study sites. Enrolment into the study continued for approximately 24 months at each of the study sites, and >4 000 cases and >5 000 controls were enrolled overall [30]. The study protocol is available online at

http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch 3

[294]. The PERCH sites were chosen in order to evaluate under-5 pneumonia aetiology in high- burden pneumonia settings, most of which had already incorporated HibCV and PCV into their vaccination schedules. Furthermore, two of the PERCH

sites (South Africa and Zambia) had a **high HIV prevalence** 105

amongst hospitalised children [293].

PERCH was therefore **designed to shed light on the** 556

anticipated shift in pneumonia aetiology in the era of access to bacterial conjugate vaccines as well as the pneumonia aetiology

in HIV-infected children in the era of antiretroviral therapy (ART) 5

[30]. In PERCH, respiratory viral pathogens contributed 63.6% (95% Credible Interval, 58.6% to 68.5%) of all pneumonia episodes in children with radiologically-confirmed disease, and bacterial pathogens were implicated in 24.6% (95% Credible Interval, 20.1% to 29.6%) of pneumonia cases [295]. Using Bayesian analysis, RSV was the predominant pathogen implicated in pneumonia aetiology in PERCH, contributing 30.7% (95% Credible Interval, 26.8% to 35.3%) to the all-site aetiology pie chart (hereafter, termed 'aetiology pie'). Pneumococcus contributed 6.1% (95% Credible Interval, 4.3% to 8.3%) to the all-site 'aetiology pie' in PERCH, and no pathogen could be attributed in 1.4% (95% Credible Interval, 0.1% to 4.3%) of cases [295]. In contrast to the GABRIEL studies, PCV vaccination coverage in PERCH was high overall, with only 17% and 13% of all cases and controls never having received a dose of the vaccine [295], which may in part explain why pneumococcus did not feature as prominently as a cause of pneumonia in PERCH [295]. The work in this thesis is based of the findings of the

PERCH study from **the South African site,** situated **at Chris Hani Baragwanath Academic Hospital** (CHBAH), **Soweto,** 2

and includes site- specific analyses on Mtb diagnostics and human cytomegalovirus (CMV) infection (as detected on whole blood) which were only done at the South African site. 1.4.4

Aetiology of Community Acquired Pneumonia in Hospitalised 972

Children in sub-Saharan Africa At least 72 **studies** conducted **in sub-Saharan Africa** 508

were published between 1970 and 2016, aimed at describing the aetiologic profile of childhood pneumonia (Appendix A, Tables A.7 and A.8 and Appendix B, Tables B.1 through B.7). Pneumonia aetiology studies performed in African paediatric pneumonia cohorts have concen- trated on culture of respiratory specimens, including IS, LA and PF for the identification of bacterial pathogens, and sampling of upper airways secretions for viral tissue culture or immun- ofluorescence testing for respiratory viral antigens, and have recently incorporated

the use of sensitive **molecular diagnostic techniques for the** identification **of** 786

respiratory viral and fungal pathogens. In 43 studies which evaluated blood culture results in children hospitalised with pneumonia (Table B.1), pneumococcus was the most consistently isolated pathogen, and when excluding three studies focussed exclusively on pneumococcal bacteraemia, pneumococcus was isolated in 833 (39.4%) of 2 116 positive blood cultures (Figure 1.6) [93, 107, 110, 115, 116, 125–127, 129, 133, 139, 149, 153, 158, 160, 164, 166, 169, 171–173, 180, 192, 196, 197, 199–203, 206, 207, 210, 216, 221, 224, 233, 242, 249, 250]. Staphylococcus aureus (271/2 116; 12.8%), H. influenzae (263/2 116; 12.4%) and Salmonella spp. (194/2 116; 9.2%) were the three most frequently isolated bacterial pathogens after pneumococcus on blood culture (Figure 1.6). Blood culture yield was low overall (2 116/24 917 total cultures; 8.5%), which highlights the poor sensitivity of blood cultures

for the aetiologic **diagnosis of** bacterial **pneumonia in children.** Notwithstanding **the** difficulties surrounding **the** use **of** 723

IS specimens in childhood pneumonia diagnostics mentioned above (page 10), these specimens have been used to evaluate the spectrum of bacterial pathogens associated with paediatric pneumonia in African studies, and in pooled analysis have a sensitivity of 33% (393 of 1 196 specimens) (Table B.2) [93, 122, 125, 166, 184, 197, 216, 240]: Klebsiella spp. play a prominent role in the 'aetiology pie' generated from the Ot9h.e7r 9.7% 3K.4LEBS 4.2 P3N9E.4U ECOL 4.2% 3.4% 4.3 91.5 91.5% 8.5% 8.5 39.4% 4.3% G4.A6S 4.6% ACINE 9.2% 12.8.4% S9A.2SP SA1U2.R8 HI1N2F.4L 2 116 (8.5%) of 24 917 blood cultures positive. Bacterial pathogens detected in 2 116 positive blood cultures. Other: other Gram positives (2.7%), other Gram negatives (2.3%), other bacteria (2.1%), PSEU (1.9%), PNEU & HINFL (0.8%). O6t.h6er 7.4 KLE22B.S6 6.6% 7.4% PSEU 7.4 32.9% 32.9 22.6% 7.4% MCAT 67.1 67.1% PNEU 20.1 20.1% 7.4% E7.C4OL 13.0% 15.5% HI1N5F.5L S1A3.U0R 393 (32.9%) of 1 196 sputum cultures positive. Bacterial pathogens detected in 393 positive sputum cultures. Other: ACINE (2.5%), other Gram negatives (2.0%), GAS (1.0%), other Gram positives (0.8%), SASP (0.3%). Ot9h.e2r 9.2%3.8% 3.8 EC4.O9L Other Gram

negatives PN42E.4U 4.9% 7.8 43.3 43.3% 56.7% 56.7 42.4% 22.7% 7.8% KLEBS 9.2% H9I.2NFL 370 (56.7%) of 652 lung aspirates positive. SAUR22.7 Bacterial pathogens detected in 370 positive lung aspirates. Other: other Gram positives (3.2%), PSEU (2.4%), GAS (1.6%), mixed organisms (1.4%), MCAT (0.3%), SASP (0.3%). Fig. 1.6: Summary of Bacteriological Testing from Children Hospitalised with Pneumonia in African Pneumonia Aetiology Studies ACINE = Acinetobacter spp.; ECOL = E. coli ; GAS = Group A β-haemolytic streptococcus; HINFL = H. influenzae ; KLEBS = Klebsiella spp.; MCAT = M. catarrhalis ; PNEU = S. pneumoniae ; PSEU = Pseudomonas spp.; SAUR = S. aureus ; SASP = Salmonella spp. pooled analysis of positive IS samples, accounting for 22.6% (89/393) positive specimens (Figure 1.6). Pneumococcus (79/393; 20.1%), H. influenzae (61/393; 15.5%) and S. aureus (51/393; 13.0%) are commonly isolated in sputum specimens from pneumonia cases (Figure 1.6), and Mtb was isolated in 3.2% (21/660) specimens. Indirect fluorescent antibody (IFA) testing of sputum specimens for Pneumocystis jirovecii (PJP) gives a reasonably high yield (70/505 pooled specimens; 13.9%), but is less sensitive than PCR testing (111/359 specimens positive; 30.9%), and 22.3% (45/202) of sputum specimens were positive for CMV on cell culture and/ or PCR (Table B.3). Studies on the

utility of LA **in the** determination **of pneumonia** aetiology **in** African **children** 420

emanate mainly from The Gambia. A synopsis of 11 such studies (including five from The Gambia) (Table B.4) totalled 652 LAs. The yield of LA (370/652; 56.7%) was higher than that of blood (263/1 844; 14.0%) for bacterial identification in these studies. Pneumococcus, S. aureus and H. influenzae were the three most prominent bacterial species cultured on LA (Figure 1.6) [90, 93, 110, 111, 114, 116, 125, 126, 129, 139, 196]. It is, however, problematic to summarise testing for atypical bacterial pneumonia pathogens and viral studies in a similar manner to that used above for bacterial pathogens, because of the different methodologies (IFA, cell culture or PCR) used in detecting these pathogens and variability in the spectrum of pathogens tested for in the studies, which leads to different denominators which challenges a summary (pooled) analysis of the data.

The atypical agents **Bordetella pertussis, Chlamydophila pneumoniae and Mycoplasma pneumoniae** 140

are detected on upper respiratory specimens in fewer than 5% of African paediatric pneumonia cases (Table B.5). Virology results on nasopharyngeal specimens are shown in Tables B.6 and B.7 (Appendix B). Human rhinovirus, CMV and RSV are the most consistently identified viral agents in African children hospitalised with pneumonia, occurring in 35.8% (5 120/14 306), 28.4% (200/705) and 22.0% (4 490/20 427) of cases, respectively. Adenovirus (3 595/19 660; 18.3%) and the parainfluenza viruses (354/5 178; 6.8%) are associated with a considerable fraction

of children hospitalised **with pneumonia in sub-Saharan Africa, and** 755

influenza has been detected in 7.4% (1 729/23 342) of paediatric pneumonia cases in the region (Tables B.6 and B.7). Adegbola et al [125] detected viral pathogens in 35% to 40% of children hospitalised with pneumonia in The Gambia, including in LA specimens and often in the context of concomitant bacterial infection. 1.4.5Childhood pneumonia in South Africa Demographic Health Surveys (DHSs) demonstrated that ARI commonly affected young children in South Africa, occurring within two weeks of interview in 19% and 12% of

children <5 years of age in 1998 **and** 2003, **respectively** 557

[296, 297]. Surprisingly, only 3% of

children <5 years of age were noted **to have** 3

had respiratory symptoms in the most recent South African DHS, which was conducted over four months (late June to early-November) in the winter and spring of 2016, and 88% of the children with respiratory symptoms were evaluated at local health facilities [298]. There has been a decline in the numbers of children presenting with ARI symptoms in the South African DHSs over time: in 1998, 915 under-5 children (from 12 247 successfully interviewed households) were noted to have suffered from ARI symptoms within two weeks of the survey, which declined to 234 children (from 7 756 households) in 2003 to 107 children (from 11 083 successfully interviewed households) in 2016 [296–298], which may reflect a true reduction in the burden of ARI impacting under-5 children in South Africa (from 75, to 30, to 10 children per 1 000 households experiencing ARI symptoms within two weeks prior to the interview) [296–298], or may be a function of the differing sampling time frames used in each of the surveys. Indeed, there is compelling evidence that, in the era post

-introduction of PCV into the South African Public Immunisation Programme (EPI-SA), 1

there has been a significant (33% to 39%) reduction in all-cause pneumonia hospitalisation in 525

young, including

HIV-infected, children [299] which has been associated with significant reductions in 122

CFR for hospitalised pneumonia [300]. Respiratory symptoms and a diagnosis of respiratory tract illness accounts for 20% to 72% of all primary care under-5 paediatric visits in South Africa [124, 301–304], and whereas the majority of these episodes are self-limiting, often translates into referral to emergency departments and hospitalisation [88, 124, 305]. Acute respiratory tract infections account for 31% (standard deviation (SD), 17.6%) of all South African paediatric hospital admissions, with CFRs ranging from 2.8% to 38.6% [83, 88, 91, 96, 99, 105, 124, 143, 151, 161, 182, 195, 209]. A pooled analysis of data from observational studies of paediatric intensive care units in South Africa reveals a median pneumonia CFR of 35.1% (Range, 11.4% to 88.0%) with

HIV-infected children having a higher odds of dying compared to those 911

that are HIV-uninfected [134, 146, 150, 157, 168, 189, 193, 204, 215, 217]. Under-5 pneumonia incidence

in South Africa was 66.8 cases per 1 000 children in 385

2012/2013, 31.4% lower than the peak average

pneumonia incidence of 97.4 cases per 1 000 children estimated in 764

2009 [306]. During the course of the under-5 pneumonia aetiology study conducted by Cohen et al [242] mentioned above, the annual incidence of pneumonia hospitalisation in Soweto ranged from 25.6 to 31.7 per 1 000 children overall, highest in the <12 month age group (84.5 to 105.3 per 1 000 children) and particularly in those that were HIV-infected (with a peak incidence of pneumonia hospitalisation of 367.5 per 1 000 HIV-infected children <12 months of age in 2009). In South Africa, using modelled data, approximately 10 000 (16%) of the 61 335 under-5 deaths in 2007 were attributed to LRTIs, which closely followed diarrhoea-related deaths (approximately 13 000 (21%) of the 61 335 deaths) as a leading cause of under-5 mortality [307]. Between 2006 and 2009, 5 930 to 9 750

South African children <5 years of age died annually with 2

a cause of death being defined as ‘influenza and pneumonia’. The contribution of these LRTIs to overall child mortality in the country declined from 15.2% (9 750 of 64 346 under-5 deaths) in 2006 to 11.7% (5 930 of 50 471 under-5 deaths) in 2009, even before the incorporation of PCV into the immunisation programme [306]. Death registry data indicates that LRTI accounted for 5 983 deaths in 2011, declining to 4 765 deaths in 2013 amongst children aged between one and 59 months in South Africa [308, 309], causing more deaths than diarrhoeal illness in 2011 and 2012 [308, 310].

In South Africa, pneumonia was the second most prevalent cause of death after diarrhoea in 726

1990,

and the leading non-neonatal cause of death in 2015 343

and 2016 [311, 312]. The SARI Study As highlighted in Section 1.4.1, a multisite observational aetiology study of

149

severe acute respiratory illness in children **and** adults **was conducted in South Africa**

from 2009 to 2012, including urban and rural settings in the era of access to PCV. Pertinent findings from the SARI Study are summarised in Table 1.5. In the SARI Study,

it was possible to calculate the incidence rate **of** severe acute **respiratory illness** 871

requiring hospitalisation at the Soweto site because of the well-defined catchment area and reasonably reliable population denominators

for children <5 years of age [242]. The highest **incidence** rates **of** 479

pneumonia requiring hospitalisation (per 100 000 children) was in the group of HIV-infected children <12 months of age which tapered off from a high of 36 745 (95% CI, 32 970 to 40 747) in 2009 to 16 893 (95% CI, 14 088 to 20 021) in 2012 [242], and within

this age group infants<4 **months of age** had **the highest** pneumonia incidence **rates.** 713

HIV-infected children had a 3.7

-fold (95% CI, 3.4 **to 4.** 0) **greater** relative **risk of** 29

hospitalisation with SARI compared to HIV-uninfected children in 2009, which trended downwards to a 1.8-fold (95% CI, 1.6 to 2.1) increased relative risk by 2012 [242]. Regardless of HIV status stratification, the

incidence of pneumonia requiring hospitalisation **decreased with increasing age** 533

group [242]. Importantly, the case definition of SARI was broader than that used in PERCH, and in children included any hospitalised child with LRTI, including 'bronchitis', 'bronchiolitis', 'pneumonia' (including non-severe pneumonia) and/ or pleural effusion, with symptom duration <7 days [242]. In contrast, enrolment in PERCH was restricted solely to cases fulfilling the WHO severe/ very severe pneumonia criteria, regardless of symptom duration. Hence, incidence rates derived in the SARI Study would be expected to be higher than in PERCH. Invasive bacterial pneumonia was diagnosed in a small proportion of SARI Study cases. Amongst HIV-infected children, 4% (12/311) had blood cultures that isolated clinically relevant pathogens, including S. aureus (n=6), S. pneumoniae

(n=4), H. **influenzae (n=1) and** K. pneumoniae **(n=1).** 834

In HIV-uninfected cases, 2% (51/2 092) isolated significant bacterial organisms on blood culture, including S. aureus (n=25), S. pneumoniae (n=13), K. pneumoniae (n=5), N. meningitidis (n=3), two each of E.coli and Streptococcus agalactiae, and H. influenzae (n=1) [242]. Although not stratified by age group, frequently occurring viral-viral co-detections in the SARI Study included human rhinovirus and adenovirus, human rhinovirus and RSV, RSV and adenovirus, and adenovirus and enterovirus [313]. The Drakenstein Study

A birth-cohort study of **child lung health,** which aims **to** 882

longitudinally follow-up children resident in two well defined peri-urban communities in the Drakenstein Local Municipality near Paarl

in the Western Cape Province of South Africa until the age **of** 754

5 years, commenced in mid- 2012 [246, 250, 314]. Pneumonia aetiology analyses for

children in their **first two years of life have** 914

been published (Table 1.6) [250]. Of 284 analysable pneumonia episodes, 60 (21.1%) of which were severe pneumonia episodes according to the 2012 revised WHO case definition, were identified amongst 235 children in this highly-vaccinated, low-HIV prevalence cohort of 967 children. Importantly, only 92 (32.4%) of the pneumonia episodes were hospitalised, and a minority (n=45, 15.8% overall) received oxygen therapy [250]. Furthermore, although 20% of the cohort was HIV-exposed in utero, only two (one case and one control) acquired HIV through vertical transmission [250]. 1. Introduction 33 Tab. 1.6: Summary of Case-Control Analysis of NP/OP PCR Data from the Drakenstein Study – Selected Pathogens [250] Pathogen All Cases (n=284; %) All Controls (n=412; %)

OR (95% CI) Severe **Cases (n=** 60; %)a **Controls (n=** 91; %)a **OR (95% CI)** **497**

a ADENO 53 (18.7) 41 (10.0) 2.15 (1.31 to 3.53) 7 (11.7) 1 (1.1) · · · BOPE 6 (2.1) 1 (0.2) 11.08 (1.33 to 92.54) 3 (5.0) 0 (0.0) · · · CMV 151 (53.2) 177 (43.0) 1.57 (1.11 to 2.21) 19 (31.7) 15 (16.5) 3.06 (1.21 to 7.69) FLU 32 (11.3) 11 (2.7) 4.13 (2.06 to 8.26) 6 (10.0) 3 (3.3) 2.99 (0.74 to 12.21) HBOV 37 (13.0) 32 (7.8) 2.29 (1.25 to 4.17) 5 (8.3) 1 (1.1) 6.53 (0.75 to 56.91) HINF 152 (53.5) 164 (39.8) 1.67 (1.20 to 2.30) 24 (40.0) 28 (30.8) 1.57 (0.76 to 3.24) PARA 35 (12.3) 26 (6.3) 2.03 (1.20 to 3.42) 6 (10.0) 5 (5.5) 1.76 (0.53 to 5.87) PJP 44 (15.5) 122 (29.6) 0.35 (0.22 to 0.55) 7 (11.7) 28 (30.8) 0.21 (0.07 to 0.63) PNEU 168 (59.2) 237 (57.5) 1.07 (0.76 to 1.48) 28 (46.7) 36 (40.0) 1.29 (0.64 to 2.62) RSV66 (23.2)17 (4.1)8.05 (4.21 to 15.38)18 (30.0)3 (3.3)25.30 (3.30 to 191.61) a Derived from reference [250] supplementary materials (Supplemental Table 7, page 7 – controls matched to severe cases); ADENO = adenovirus; BOPE = B. pertussis ; CI = confidence interval; CMV = human cytomegalovirus; FLU = influenza virus A, B and C; HBOV = human bocavirus; HINF = non-type b H. influenzae ; OR = odds ratio; PARA =

parainfluenza virus (types 1, 2, 3 and 4 **130**

combined); PJP = P. jirovecii ; PNEU = S. pneumoniae ; RSV = respiratory syncytial virus. In case-control analysis of Drakenstein Study participants, in which controls were incidence- density

matched to pneumonia **cases by birth** date, age **and study site,** **860**

NP/OP swabs were subjected to multiplex PCR testing for respiratory pathogens and the pathogen profiles detected in cases and controls compared. Of 31 pathogens which

were included in the analysis, eight were **associated with** case status **and** **899**

only P. jirovecii was significantly associated with control status (Table 1.6). Amongst cases with WHO-defined severe pneumonia, only RSV (OR 25.30; 95% CI, 3.30 to 191.61) and CMV (OR 3.06;

95% CI, 1. 21 **to** 7.69) **were significantly associated with** **305**

case status (Table 1.6). Although the study was not powered to investigate

the aetiology of hospitalised **pneumonia,** particularly **in HIV-infected children,** **35**

the Drakenstein Child Health Study – through repetitive sampling of the nasopharynx – provides insight on the temporal changes

in the upper respiratory tract microbiome **and** lung health **of children** **922**

residing in a developing country setting [315]. 1.5South Africa's HIV Epidemic No appraisal of childhood pneumonia in South Africa would be complete without reference to the impact that

human immunodeficiency virus and **acquired immunodeficiency syndrome (HIV/AIDS)** has had on **the** state **of** health **in** **689**

the country. Over one quarter (6.8 million) of sub-Saharan Africa's 25.8 million HIV-infected individuals reside in South Africa [316], the country which has been most severely impacted by the HIV epidemic. Although it was decided in 1985 that acquired immunodeficiency syndrome (AIDS) ought not to be classified as being a notifiable condition in South Africa [317], regular reporting of

the number of identified AIDS **cases was** conducted **by the** **902**

Department of Health from April 1990 [318] to end-November 1995 by which time 8 784 AIDS cases, 978 (11.1%) of which were diagnosed in

children <5 years of age, had **been reported** [319]. A survey **of** **92**

antenatal HIV seroprevalence conducted in the Pretoria-Witwatersrand-Vereeniging Area from May 1987 to October 1988 elucidated a positivity rate amongst black clinic attendees of 0.1% overall (96 of 84 527), with steadily increasing seroprevalence over the 18 month study time-period and a doubling time of six months [320], and gave impetus to a series of national antenatal HIV seroprevalence surveys, the first of which was conducted in 1990, which revealed a 0.8% prevalence of the infection [321]. Antenatal seroprevalence had doubled (1.5%) by 1991, indicating that although the country appeared to be

in the early stages of a widespread **HIV epidemic (with** **187**

an estimated 200 000 adults being infected) [322], rapid growth of the epidemic was occurring [323]. By end-April 1994, when South Africa transitioned peacefully to democracy, the antenatal HIV prevalence was 7.6% [324] and 461 paediatric AIDS cases

<5 years of age had **been reported** to **the** National Department **of** **92**

Health [325]. The antenatal HIV seroprevalence rate peaked at 30.2% in 2005, and has remained near 30.0% since then [326]. In 2001, some years after results of clinical trials implementing ART

for prevention of mother- to-child transmission (PMTCT) of HIV **739**

had been published [327–330] and the South African government persisted in obstructing efforts to implement strategies of HIV/AIDS prevention and care which entailed the use of ART, legal action compelling the Department of Health to establish a PMTCT programme was entered into [331, 332]. The Constitutional Court ruled in favour of the establishment of a PMTCT programme in 2002 [333]. A country-wide PMTCT programme was officially implemented in 2002, achieving

reductions in transmission of HIV from mother-to-child **811**

from 9.6% to 2.8% between 2008 and 2011 [334]. It was not until March 2004, in response to mounting pressure from the international community, civil society and health care professionals [335], that a comprehensive national

roll-out of ART was implemented **in South Africa,** albeit with initial **sub-** **919**

optimal coverage of those in need of treatment [336].

South Africa currently **has the world's largest** ART **programme** **287**

[337], which in 2015 catered for 3 710 130 (48.5%; lower-to-upper estimate, 46.1% to 51.6%) of 6 984 580 HIV-infected persons, 235 192 (6.4%) of whom were

children under 14 **years of age** [338]. Revised estimates **of South African** **507**

AIDS-related deaths between 1997 and 2010 suggest that 2.8 million people died of AIDS during that time period, 1.3 million of which occurred in the years 2000 to 2005 [339]. South African AIDS deaths peaked in 2006 (283 000 deaths), and started to decline thereafter [339]. It is estimated that, had a comprehensive ART and PMTCT programme been implemented in South Africa in the year 2000, 330 000 lives and 3.8 million person-years would have been saved, 171 000 new HIV infections would have been prevented and 35 000 vertically-acquired infections amongst infants would have been averted by 2005 when the government ART roll-out was beginning to gain impetus [340, 341]. 1.5.1Paediatric AIDS in South Africa The first documented South Africa paediatric AIDS case, a male from KwaZulu-Natal who presented with diarrhoea and wasting syndrome, was reported to the Department of Health in June 1988 [342]. In 1989, paediatric AIDS cases were being identified in Soweto, a densely populated urban residential area south-west of Johannesburg [343, 344]. By 1992, 110 HIV- infected children were treated at CHBAH, and this

increased further to approximately 950 cases by 1996 with high numbers of paediatric admissions, a shift towards more infectious-disease related admissions, prolonged hospital stays and increasing in-hospital mortality rates, all of which placed considerable strain on the hospital's resources [151].

Lower respiratory tract infections were **the leading cause of death** in South African **under-** 143

5 children and 60% of under-5 deaths were HIV/AIDS related in 2000 to 2004 [345, 346], before the National ART programme was established. Two studies which have reappraised

infant and child mortality rates **in South Africa** in **the** 909

pre-ART era indicate that there was an unanticipated peak of infant mortality at two to three months of age amongst children hospitalised at public sector hospitals, and that most of the HIV-associated deaths were mis-assigned as being caused by LRTIs [347, 348]. These findings suggest that respiratory tract infections, possibly caused by opportunistic organisms – especially P. jirovecii and/ or CMV [135, 174, 344] – were frequently encountered in young HIV-infected infants in the pre-ART era and may still affect those

children in the current **era of access to ART** 5

if initiation of treatment is delayed. Although ART in the treatment of HIV infection had been used to good effect in paediatric patients

in Europe and North America since the late- 470

1980s [349], and combination highly active ART had

been demonstrated to improve immunologic **and clinical outcomes in** 511

children by the mid-1990s [350], it was not until the mid-2000s that this life-saving medication was made available for widespread use in South Africa. By 2005, there were 300 000 children <15

years of age living with HIV in South Africa **(10%** of **the** 785

sub-Saharan African paediatric HIV-infected burden) [351], the under-5 mortality rate was 74.4

per 1 000 live births (having peaked **at** 77.8 **per 1 000 live births in** 645

2002) [46, 307], and children were starting to access ART through the national roll-out programme. Impetus for initiation onto ART increased dramatically from 2005, when 2 412 children were registered as having been initiated onto ART at

United States President's Emergency Plan for AIDS Relief (PEPFAR) 712

-funded facilities nationwide. By 2010, almost 80 000 children were accessing ART at those facilities [352]. Whereas the initial emphasis on initiation of ART was focussed on children with severe immun-osuppression and/ or advanced clinical stage of HIV infection, recommendations for initiation of ART shifted towards fast-track onto therapy of any infant regardless of degree of immunosuppres- sion or clinical stage, largely in response to the pivotal

Children with HIV Early Antiretroviral Therapy (CHER) Trial, published in 2008 476

[353]. In the

CHER study, which was conducted at **two** treatment sites **in South Africa,** 476

HIV-infected infants between 6 and 12 weeks of age with CD4+ 719

T-lymphocyte percentages of ≥25 were randomised either to receive ART as per standard of care (i.e., only to start ART when CD4+ T-lymphocyte percentages dropped below 25%), or to provide access to ART (lamivudine, zidovudine and lopinavir-ritonavir) at enrolment. The trial

was terminated at the recommendation of the safety monitoring board 765

when, upon review of the deaths which had occurred from study commencement (August 2005) until completion of participant enrolment (in June 2007), there was an overwhelming survival advantage

(Hazard Ratio 0.24; 95% CI 0.11 to 0.51) 691

associated with expedited access to ART [353]. In 2008, the WHO recommended that any HIV-infected infant be initiated onto ART [354] and subsequent guidelines (2010 and 2013) encourage fast-track onto ART of any HIV-infected child <24 months and <60 months, respectively [355, 356]. In 2012, 166 000 (45.0%) of the estimated 369 000

HIV-infected children <15 years of age were accessing ART 951

through the South African national ART programme [357], and these were significantly younger and had less advanced clinical and immunologic status at ART initiation than were children accessing ART in 2004 through 2009 [358]. 1.5.2HIV-exposure

as a Risk Factor for Pneumonia Morbidity and Mortality The 920

first case series describing an unanticipated increase in infectious-disease related morbidity and mortality amongst African children that were HIV-exposed but -uninfected were published in the early 1990s [359]. This phenomenon

has been variously attributed to disturbances in the development of the adaptive immune system which has been exposed to 682

HIV antigens in utero [360], immune activation and inflammation resulting from intrauterine exposure to opportunistic pathogens, including CMV, antenatal exposure to ART which may precipitate preterm delivery and have mitochondrial toxic effects, and probability of living in families with a greater degree of instability (including orphanhood and poverty) and exposure to infectious diseases [359]. With a birth cohort of approximately 1.0 million infants annually [361], and an antenatal HIV exposure rate of 30% [326] it is anticipated that approximately 300

000 HIV-exposed infants are born in South Africa each year. 87

With a vertical transmission rate of 3% [362], 9 000 HIV-infected and 291 000 HIV-exposed, uninfected (HEU) were born

per year in South Africa in 2012 and 2013. Within the context of 23

the SARI study, Cohen et al [363] observed a considerably

higher incidence rate of LRTI in HEU children compared to HIV-unexposed children 10

(incidence rate ratio (IRR) 1.4; 95% CI, 1.3 136

to 1.5), with a greater burden of LRTI attributable to RSV and HMPV amongst HEU cases compared to HIV-unexposed children. Furthermore, there was a 12-fold (95% CI, 1.7 to ∞) higher odds of death due to LRTI associated with RSV in HEU cases compared to HIV-unexposed cases [363]. 1.6The Evolution of the South African Immunisation Programme: 1963 to 2013 Immunisation is widely regarded as

one of the most important public health interventions of the 20th Century 709

[364–368].

In 1974, the WHO initiated the Expanded Programme on Immunisation (EPI), 925

which targeted six infectious agents (B. pertussis, Clostridium tetani, Corynebacterium diphtheriae, Mtb and the viral agents causing measles and poliomyelitis) [369–372]. At the time of implementation of the EPI,

fewer than 5% of the world's children 884

had been immunised against these pathogens [370]. By 1980, 50 (25.8%) of 194 countries and territories had instituted a method of documenting EPI coverage of bacillus Calmette-Gu´erin (BCG), the

third dose of diphtheria, tetanus toxoid and pertussis vaccine (DTP3) and measles-containing vaccine (MCV), and this increased to 582

133 (68.6%) countries by 1990 [373].

Efforts to accelerate EPI coverage, through the 'Universal Childhood Immunisation by the 905

year 1990' programme which was promulgated by WHO in 1985 [369], achieved the universal coverage target only by a narrow margin [370, 371] with 107 countries not having reached the target in 1990 [374]. The ambitious universal coverage target was for 80% of infants to have been immunised with at least

one dose of BCG and MCV, and three doses each of diphtheria, tetanus toxoid and pertussis vaccine 661

(DTP) and oral polio vaccine (OPV), before they reached their first birthday [375]. South Africa, suspended from membership in the WHO since 1964 in response to its governmental policy of apartheid [376, 377] and not readmitted as an active member in the Organization until 1994 [378], developed its vaccination policy largely in parallel with the EPI (Figures 1.7 and 1.8). Recommendations for immunisation with trivalent OPV and BCG vaccine of infants under six

months of age were implemented in South Africa in 1963 and 261

1973, respectively [379, 380], both of which ante-dated the year (1977) in which the WHO recommended use of these vaccines [381]. Before then, there was no co-ordinated immunisation programme in South Africa, and DTP and BCG vaccination were administered in non-systematised fashion as part of public health activities in the country [382, 383]. Measles vaccination and immunisation for diphtheria were WHO EPI (1974) BCG Diphtheria MeaslesPertussis Polio Tetanus WHO EPI Plus (1994) BCG Diphtheria MeaslesPertussis Polio Tetanus Hepatitis B Yellow Fever WHO Position Papers HibCV - 1998, 2006, 2013 PCV - 2003, 2007, 2012 South Africa suspended from WHO (1964 to 1994) Soweto PCV9 and RV Trials 19701980199020002010 SA (1963) Polio vaccination legislated SA (1994) Hepatitis B vaccine legislated SA (1973) BCG vaccination legislated SA (1999) HibCV legislated SA (1975) Measles vaccination legislated SA (2009) PCV and RV legislated SA (1979) Diphtheria vaccination legislated SA (1984) BCG and Polio vaccination compulsory by law SA (2011) PCV7 superseded by PCV13 1. Introduction 39 Fig. 1.7: Evolution of the South African Expanded Programme on Immunisation: 1963 to 2013 BCG = bacillus Calmette-Gu´erin; EPI = Expanded Programme on Immunisation; HibCV =

H. influenzae type b conjugate vaccine; 195

PCV = pneumococcal conjugate vaccine; PCV7 = 7-valent PCV; PCV9 = 9 -valent PCV; 742

PCV13 = 13-valent PCV; RV = rotavirus vaccine; SA = South Africa; WHO = World Health Organization. Age Groups 1979 1987 1995 1999 2009 Birth

6 weeks 10 weeks• 14 weeks 4 **months** 5 **months** • 6 **months** • 7 **months** • 8 **months** 9 **months + + + ••• • • • • 18 months** 5 **years** 6 **years** 12 **years** 543

• I ••• I I I 1. Introduction 40 BCG DTP • DTP-IPV//HibCV• DTP/Polio HBV + HibCV • MCV OPV PCV RV I Td
Fig. 1.8: South African Expanded Programme on Immunisation Schedules: 1979 to 2009

BCG = bacillus Calmette- Gu´erin; **DTP = diphtheria, tetanus** toxoid **and pertussis vaccine;** 763

DTaP-IPV// HibCV = **diphtheria, tetanus** toxoid, **acellular pertussis, inactivated polio** with H. **influenzae type b** 1

conjugate vaccine; DTP/Polio = diphtheria, tetanus toxoid and pertussis vaccine, and

oral polio vaccine; HBV = **hepatitis B vaccine;** HibCV = H. **influenzae type b** conjugate **vaccine;** 129

MCV = measles-containing

vaccine; OPV = oral polio vaccine; PCV = pneumococcal conjugate **vaccine; RV = rotavirus vaccine; Td = tetanus** toxoid, low-dose **diphtheria;** 1

Shaded areas in 1979 vaccination schedule represent age ranges at which the relevant vaccine dose was administered. legislated in South Africa in 1975 and 1979, respectively [384, 385]; however, by 1984 only BCG and polio vaccination was considered compulsory by law in South Africa [386]. By 1979, immunisation policy in South Africa recommended that BCG (a single dose, administered at any time from birth to four months of age), DTP and OPV (three doses, administered at any time from 2.5 months to eight months of age) and MCV (one dose, administered from six to nine months of age) be given to all infants, although there was considerable deviation in timing of administration of these vaccines [387]. The approach to childhood immunisation was fragmented, even within district health services [388], and intermittent poliomyelitis [379, 389], measles [384, 390, 391] and pertussis [383] outbreaks in the 1980s were a pertinent reminder that a co-ordinated approach to childhood vaccination was a matter of urgency. The Road-to-Health Card (RTHC), a tool introduced in 1987 to monitor each child's growth trends over time, and his interactions with primary health care services, included a field for recording dates of administration of up to three doses of BCG, five each of DTP and OPV, and two doses of MCV but prescribed no particular age at which immunisations should be administered, so as to accommodate children accessing the immunisation services 'out of phase' with the recommended schedule [392]. This vaccination package was made freely available to children in South Africa from 1987 [393, 394]. In 1995, after readmission of South Africa to the WHO, EPI-SA consisted of a dose of BCG

at birth, and DTP administered **at 6, 10 and 14 weeks of age with** a **booster** dose **at 18 months and** 545

tetanus toxoid, low-dose diphtheria vaccine (Td) administered at 5 years of age; OPV was administered at

birth, 6, 10, 14 weeks, 18 months and 5 years; 733

MCV at 9 and 18 months, and

hepatitis B vaccine (HBV) **at 6, 10 and 14 weeks** 1

[395]. 1.6.1Bacterial Conjugate Vaccines against Pneumonia Pathogens in

the South African Expanded Programme on Immunisation (EPI-SA) Maturation in **the** development **of** 674

the South African vaccination schedule against pneumonia pathogens occurred with the inclusion of polysaccharide-protein HibCV in 1999 [396] and PCV a decade later [397, 398], following the WHO

recommendation that these vaccines be incorporated into the vaccination schedules of countries with the capacity to do so [399, 400], and a pivotal efficacy trial of a

9-valent pneumococcal conjugate vaccine (PCV9) which **was conducted in Soweto** from 1998 **with** 1

long-term follow-up of trial 496

participants until 2006 [401, 402]. Vaccination against

Haemophilus influenzae type b in South Africa In 55

1999,

South Africa became **the** second **African country to introduce** HibCV **into its EPI** 232

after The Gambia [403], where it had been introduced in 1997 [404]. The vaccine was administered in

a three-dose primary series, coinciding **with** 520

DTP vaccination at six,

10 and 14 weeks of age with **no booster** dose, **and** 766

no catch-up for unvaccinated older children [405]. The incidence (per 100 000 children) of invasive Hib disease in Cape Town in the early 1990s was 47 (95% CI, 39 to 57) in under-5s, and highest in infants (169 per 100 000) and black children (336 and 104 per 100 000 in infants and under-5s, respectively) [127]. A quarter of children hospitalised with invasive H. influenzae disease presented with pneumonia [127], in a community with background nasopharyngeal Hib carriage rates of 4.7% in healthy children [406]. Another study, conducted in Soweto, elucidated high

incidence rates of invasive Hib disease 984

and bacteraemic pneumonia in HIV-uninfected infants (again, 170 per 100 000) and exceptionally high rates of disease in those who were HIV-infected (1 003 per 100 000) in the pre-ART era [170]. Based on the

incidence rates of invasive Hib disease 496

generated by the Cape Town study, it was estimated that >5

000 cases of invasive Hib disease occurred annually in South Africa in **the** 703

era before incorporation of HibCV into the EPI [405]. Invasive disease caused by Hib had been notifiable in South Africa since 1994 [407], but was grossly under-reported. Only 262 cases of invasive Hib disease and 14 deaths (CFR 6.2%), and considerable disparity in case detection between provinces, were notified to the National Department of Health in the five years prior to the inclusion of HibCV into the EPI-SA [408]. In a pneumonia aetiology study conducted over

a 12-month period in Soweto **two years** prior **to** 932

incorporation of HibCV into the EPI, and one year before the vaccine was implemented for use in the birth cohort as part of the afore-mentioned PCV9 efficacy trial in which HibCV was administered to both PCV9 and placebo recipients (for the benefit of controls participating in the study) [401], HIV-infected children had a significantly higher relative risk (21.4; 95% CI, 9.4 to 48.4) of bacteraemic Hib pneumonia compared to HIV-uninfected children [158]. This study also capitalised on the fact that infants participating in the Soweto PCV9 efficacy trial were benefitting from receipt of HibCV administered at six,

10 and 14 weeks of age, and compared rates of invasive 738

Hib disease amongst trial participants who had received HibCV to invasive Hib disease rates occurring in the (HibCV-unvaccinated) birth cohort from the previous year [170]. There was significantly reduced efficacy of HibCV in HIV-infected children (43.9%; 95% CI, -76.1% to 82.1%) compared to those who were HIV-uninfected (96.5%; 95% CI, 60.3% to 91.8%) [170]. The mean age of HibCV failure was 8.9 ± 3.9 months regardless of HIV infection status [170]. Strong evidence for reduced effectiveness of HibCV in HIV-infected children was further generated in an immunogenicity study, which revealed that HIV-infected infants (in the pre-ART era) developed significantly lower mean geometric titres of anti-Hib capsular polysaccharide antibody one month after vaccination with HibCV than did HIV-uninfected infants (1.95 µg/mL (95% CI, 1.20 to 3.14 µg/mL) versus 10.75 µg/mL (95% CI, 8.52 to 13.72 µg/mL), respectively) [409]. HIV-infected infants also had less robust serum bactericidal activity of vaccine-derived antibody and it was estimated that they were at 35-fold (95% CI, 14.6 to 84.6) greater risk of HibCV failure compared to HIV-uninfected infants [409]. HibCV effectiveness

was estimated to be 55% (95% CI, -4.6% to 80.3%) in HIV- 772

infected children, and 91% (95% CI, 79.4% to 95.8%) in those that were HIV-uninfected [409]. Additionally, a bimodal age pattern of vaccine failure (defined as being invasive Hib disease occurring in a fully-vaccinated child, i.e. after receiving three doses of HibCV, beyond 14 days of the third dose of vaccine), occurring at 6.3 ± 2.9 months and 32.5 ± 13.0 months was noted in HIV-infected vaccinees, whereas all HIV-uninfected vaccine failures occurred in children under nine months of age [409]. The 1998 WHO position paper on the use of Hib vaccination highlighted the fact that, as most

invasive Hib disease occurs in children under 18 months of age in 500

developing world settings, a primary series of vaccination without

a booster dose at 12 to 18 months could substantially reduce the 529

burden on invasive Hib disease [399]. This was emphasised again in the 2006 WHO position paper on Hib vaccination, which recommended

that a three -dose primary series of 520

HibCV should be given in conjunction with DTP vaccine in all developing countries, and reiterated the opinion that the need for a booster dose (administered at 12 to 18 months) required further investigation [410]. Within five years (mid-1999 to mid-2004) of incorporation of HibCV into EPI-SA, there was a 65% reduction in invasive Hib disease in infants <12 months of age, and a 79% reduction in

children between one and five years of age, as detected by 757

laboratory surveillance in South Africa [411]. Although data on vaccination status were incomplete, only one case of vaccine failure was documented through this surveillance. Of note, was that the median age at

hospitalisation with invasive Hib disease was 9 months in 241

children <5 years of age, and 154

that less robust reductions in invasive Hib disease occurred in settings with high HIV prevalence [411]. National surveillance likely underestimated the incidence of invasive Hib disease, as incidence rates in infants were significantly lower (55 per 100 000) in the first year of vaccine rollout (1999 to 2000) compared to incidence rates reported in the early 1990s (169 per 100 000) [127], despite incomplete vaccine coverage (estimated to be 64% for a third dose of HibCV by one year of age in 2000) [411]. Extended nation-wide

surveillance for invasive Hib disease in South Africa 976

from 2003 to 2009 highlighted a significant increase in invasive Hib disease, with an appreciable proportion of invasive cases (51%) amongst

children who had received three doses of HibCV. 241

Vaccine failures occurred in HIV-infected and HIV -uninfected children, with half of 339

those >18 months of age being HIV-uninfected [412]. Trends towards increasing invasive Hib disease had been appreciated as early as 2005, through national surveillance activities, and by 2009 the EPI-SA schedule was amended to include

a booster dose of HibCV at 18 months of age 1

in tandem with transitioning

from whole-cell to acellular pertussis containing combination vaccines 386

[412]. From 2010 to 2014, the annual

number of invasive Hib cases in children 496

<5 years as detected by nation-wide laboratory surveillance had more than halved (from 82 to 30 isolates), with invasive Hib incidence rates in infants declining from 5 to 2 per 100 000 children [413–417]. Vaccination against Streptococcus pneumoniae in South Africa

Streptococcus pneumoniae was the commonest bacterial isolate observed in children 233

hospitalised with bacteraemic CAP in the pre-ART, pre-PCV era in South Africa and HIV-infected children had a 43-fold (95% CI, 20.7 to 90.2)

greater risk of developing bacteraemic pneumococcal pneumonia compared to HIV-uninfected children [158]. In 40

2007/ 2008, when 74% of South African

HIV-infected children in need of ART were accessing treatment, the 232

risk of bacteraemic pneumococcal pneumonia in under-5s remained 27-fold (95% CI, 18.2 to 39.0)

greater in HIV- infected children compared to HIV -uninfected children [418]. The efficacy trial of 96

PCV9 which was conducted in Soweto from 1998 to 2000, with follow-up of participants until October 2006, established for the first time

the efficacy of PCV in a setting with high HIV prevalence 700

[401, 402]. Although vaccine efficacy was decreased in HIV-infected children the potential public health benefit of vaccinating against

pneumococcal disease in this group of children was anticipated to 849

be considerable, because the greatest

burden of pneumococcal disease was concentrated in children who are HIV infected 848

[260]. The vaccine trial investigated the

efficacy of PCV9 in a cohort of 39 836 children who were born in 831

Soweto between 1998 and 2000, randomised to receive either PCV or placebo at six, 10 and 14 weeks of age [401].

At the time of study conduct, there was no access to ART 683

for

prevention of mother-to-child transmission of HIV and the estimated vertical transmission rate of HIV was 646

26%. The vertical transmission rate, coupled with the antenatal HIV seroprevalence of 25%, imputed that 6.5% of trial participants would have been infected with HIV by their mothers [260]. HIV infection status was determined in trial participants who were hospitalised for any reason during the course of the study, through 24 hour active surveillance at the admissions ward at CHBAH, the only hospital in Soweto catering for the more than 90% of the local population without medical insurance [401]. In intention-to-treat analyses, PCV9

efficacy against vaccine-serotype invasive pneumococcal disease (IPD) was 83% (95% CI, 39% to 97%) in HIV-uninfected children, 1

65% (95% CI, 24% to 86%) in HIV-infected children 1

and 72% (95% CI, 47% to 87%) overall at

2.3 years of follow-up [401]. Vaccine efficacy against radiologically-confirmed pneumonia was 17% (95% CI, 1

4% to 28%) in all children, regardless of

HIV infection status, at 2. 3 years of 185

follow-up [401]. At 6.2

years of follow-up, vaccine efficacy against vaccine-serotype IPD 1

had declined amongst the

HIV-infected children (39%; 95% CI, 520

-8% to 65%) but

remained relatively unchanged in the HIV-uninfected cohort (78%; 95% CI, 34% 1

to 93%) [402]. Lower vaccine efficacy

in HIV-infected children compared to those that were HIV-uninfected 35

was likely due to less robust immunogenicity of PCV9 (as measured approximately one month after administration

of the third dose of vaccine) in HIV-infected children, particularly in those with 676

clinically more advanced HIV disease [419]. The 2003 WHO position paper on pneumococcal vaccine, whilst highlighting the impact that introduction of 7

> **-valent pneumococcal conjugate vaccine (PCV7) in 2000** had **on the** burden **of** **705**

IPD

> **in the United States,** cautioned that **the** prohibitive cost **of the vaccine and** **143**

the possible need for its reformulation in order to accommodate pneumococcal serotypes prevalent in developing world settings, would need to be considered before recommendations could be made regarding wide-spread use of PCV in LMIC immunisation programmes [420]. The favourable outcomes of the Soweto PCV9 trial [401], and those of a similar

> **trial of PCV9** efficacy which **was conducted in The Gambia** **954**

from 2000 to 2003 (in which three doses of PCV9 or placebo were given at approximately 11, 17 and 24 weeks of age) [259], helped to consolidate the benefit of PCV vaccination of children in high- and low-HIV prevalence settings in the sub-Saharan African context. A revised WHO position paper on PCV vaccination from 2007 highlighted that over 400 000 childhood

> **deaths could be averted each year through routine** **368**

infant vaccination using PCV, and that the vaccine should be considered as priority for inclusion into the vaccination schedules of countries in which the under-5

> **mortality rate was greater than** 50 **per 1 000 births** **143**

[400]. The WHO recommendation in 2007 was that PCV be given, concurrently with DTP and HBV, in three doses to infants with no booster dose [400]. In 2009, South Africa incorporated PCV into its national immunisation programme, being the first African country to do so [398]. PCV7 was used in the initial phase of the South African pneumococcal vaccination schedule which transitioned to

> **13-valent pneumococcal conjugate vaccine (PCV13) in** 2011 [421]. **The vaccine** **771**

was administered in a novel two-dose prime at six

> **and 14 weeks and a booster dose at** nine **months of age** **457**

[398]. This schedule was adopted to limit the cost of the vaccine series (by avoiding a three-dose primary series), whilst also aiming to optimise vaccine effectiveness amongst older children (through provision of the 9-month booster dose). The potential effectiveness of this schedule was corroborated in

> **that the two-dose (spaced two months apart)** **185**

and three-dose (spaced one month apart) primary series of PCV yielded similar immunogenicity in infants [422, 423], and the booster dose elicited an increase in

> **antibody responses to pneumococcal** serotypes included **in the** **185**

primary vaccination schedule [424]. Furthermore, this schedule aimed to address the waning efficacy in

> **the absence of a booster dose** **185**

> **of PCV in HIV-infected children** as observed **in the** **96**

efficacy study [402]. The

two-dose primary series, followed by a booster dose administered 73

between nine and 15 months, was noted to be an alternative PCV dosing schedule in the 2012 WHO position paper on pneumococcal vaccination [425]. 1.6.2Vaccination Coverage in South Africa

WHO and United Nations Children's Fund (UNICEF) modelled estimates of 99

South African EPI vaccine coverage are regularly updated [426, 427], and indicate that in 2011 through 2013, 69%, 65% and 73% of infants in the country had received DTP3 and that 62%, 70% and 69% had received a third dose of PCV in 2011, 2012 and 2013, respectively. Since the late 1990s, official estimates (those reported by national authorities) of vaccine coverage have invariably been higher than the WHO/ UNICEF estimates (Figure 1.9). 1.6.3Implications of Widespread Vaccination Coverage for Pneumococcus and Hib on Pneumonia Aetiology Effective vaccination against pneumococcus

has been shown to decrease nasopharyngeal carriage of vaccine-type 54

pneumococci in HIV-infected and -uninfected vaccinees and their close contacts [428, 429], and to limit the rates

of invasive disease caused by vaccine -serotype pneumococci even in the 480

unvaccinated as a benefit of herd protection [421, 430–434]. There is mounting evidence Fig. 1.9: WHO/ UNICEF Estimates of Vaccination Coverage in South Africa [426, 427]

BCG = bacillus Calmette- Gu´erin; DTP3 = third dose of diphtheria, tetanus, pertussis vaccine; Hib3 = third dose of H. influenzae type b vaccine; MCV1 = first dose of measles-containing vaccine; PCV3 = third dose of 452

pneumococcal conjugate vaccine; = official vaccine coverage estimates; = WHO vaccination coverage estimates. that non-vaccine type pneumococci are implicated as the major cause of in IPD amongst children and adults in the era post-introduction of PCVs, which may in turn off-set the positive impact of PCV7 and PCV13 in settings with widespread PCV coverage [435–439]. Studies documenting similar reductions in nasopharyngeal carriage and herd immunity following introduction of HibCV into national immunisation programmes are less robust than for PCV [440– 442], although sustained benefit from widespread coverage using HibCV has been demonstrated [443–445]. There has been concern regarding the proportional increase

of non-type b H. influenzae as a cause of 412

invasive H. influenzae disease in the 390

HibCV era [446–448]. Now that effective vaccines targeting the dominant bacterial pneumonia pathogens – pneumo- coccus and Hib as described from the pre-vaccination era literature – are widely available, it is anticipated that there would be a shift in spectrum of pneumonia aetiology in countries that have included PCV and HibCV into their immunisation programmes [293, 449–451]. 1.7Restatement of the Problem

Globally, pneumonia is the leading cause of death in children <5 years of age and in South Africa it is the leading non-neonatal cause of 483

death in this age group [311].

The burden of childhood pneumonia in South Africa is compounded by 974

HIV infection and -exposure, both of which have been shown to increase the incidence of pneumonia hospitalisation and mortality [363, 452]. Foundational pneumonia aetiology studies in South Africa were

conducted in the era before HibCV and PCV were incorporated into the EPI-SA, and before PMTCT and ART programmes had been implemented and optimised

for the prevention of vertical **transmission of HIV and the** treatment **of** 110

those infected with HIV [158, 166, 453]. A comprehensive multicentre study of paediatric and adult severe acute respiratory illness

in South Africa evaluated **the burden of disease** caused by **a** limited repertoire **of** 1

predominantly respiratory viral pathogens in patients hospitalised

in the public health sector in South Africa, 843

but did not include a control arm to facilitate interpretation of study findings particularly for severe acute respiratory illness attributed to respiratory viral causes [242, 269]. Furthermore, a longitudinal study of childhood pneumonia aetiology is currently underway

in the Western Cape Province of South Africa 13

[250], however very few of the cases met the criteria of severe pneumonia and fewer were hospitalised. Studies are needed to advance our current understanding of hospitalised under-5 pneumonia aetiology globally, as well as

in South Africa. South Africa, with its high **burden of** HIV **disease and** 753

access to functional EPI-SA, PMTCT and ART programmes and with a rich evidence base of prior research into childhood pneumonia epidemiology, is a suitable setting in which to conduct a state-of-the-art pneumonia aetiology study. 1.8Aim and Objectives The aim of the series of studies compiled herein was to

describe the aetiology of pneumonia in children between **the** ages **of** 787

one

and 59 months of age, hospitalised **with WHO-defined severe** and **very severe pneumonia** 2

in Soweto, South Africa using a

case-control study design **(within the** context **of the** PERCH **Study).** The objectives **of** 782

the series of studies were to: 1. Describe the aetiology of under-5

severe and very severe pneumonia (as defined **by the WHO** 2005 classification, **Table** 225

1.1) in HIV-uninfected children, stratified by HIV-exposure status; 2. Describe the aetiology of under-5

severe and very severe pneumonia (as defined **by the WHO** 2005 classification, **Table** 225

1.1) in HIV-infected children; 3. Determine the pathogen-specific incidence rates for pneumonia hospitalisation, stratified by age-group, HIV-infection and -exposure status in Soweto, Gauteng Province; 4. Determine the utility of gastric aspirates (GAs) and IS in the diagnosis of

2

culture-confirmed PTB **in children** hospitalised **with severe or very severe pneumonia;**

5. Conduct a lung-biopsy

study to determine the aetiology of pneumonia in **232**

children dying from pneumonia, inclusive of cases not enrolled in PERCH; 6. Evaluate the role of CMV in pneumonia aetiology in a setting of high HIV-infection and -exposure. 1.9Overview of this Thesis Objectives listed in Section 1.8 are covered in separate chapters within the body of this thesis, following after Chapter 2 which describes the methodology by which the studies were conducted. Chapter 3 details the number of cases and controls enrolled into PERCH at the South African site, and in two main sections (Section 3.2 and Section 3.3), explores the differences in clinical presentation between cases and controls, cases stratified by chest radiographic findings, pneumonia severity and outcome, and describes the basic microbiology of pneumonia in the cases in

HIV- uninfected and HIV-infected children, respectively. The most important Chapter **in** **318**

this thesis – and the one most densely populated with data – is Chapter 4, in which differing organism prevalence on NP/OP PCR and lytA on whole blood observed in cases and controls,

stratified by HIV-infection and -exposure status, are described. **The** **136**

important aspect of this Chapter is Section 4.2, detailing the logistic regression model outputs of the contribution of organisms identified in NP/OP swabs and whole blood (for lytA) towards case-status. The attributable fraction method [454] was used to infer the proportion of pneumonia episodes associated with each organism at a population level. Chapter 5 details pneumonia incidence overall, and stratified by the major implicated organisms, as derived from the 'fraction of association' (FA) outputs that are presented in Chapter 4. Incidence rates stratified by age group and

HIV-infection and -exposure status, and **the** relative risk **of** disease between **HIV-** infected **and** **136**

-uninfected children, and HEU children and HIV- unexposed children are described. Chapter 6 contains the results of an analysis that explored the utility of IS and GAs in assisting the diagnosis of PTB in the South African PERCH cohort. Furthermore, an analysis of Mantoux test positivity in cases and controls is presented, in order to explore whether Mtb infection

was a risk factor for pneumonia in **319**

PERCH. Chapter 7 describes the findings of a post-mortem lung biopsy study at the South African PERCH site. Chapter 8 interrogates the utility of CMV whole blood PCR in establishing the cause of pneumonia as being due to CMV in the South African PERCH cohort, after taking into consideration the findings of the post-mortem lung biopsy study. Finally, Chapter 9 integrates and summarises the pertinent findings from the body of work presented herein and conclusions and recommendations for further research are presented in Chapter 10. 2 Methods 2.1PERCH Study Conduct at the South African Site The studies presented in this thesis emanate from PERCH activities conducted at the South African PERCH site, at CHBAH, Soweto, Gauteng Province. 2.1.1The PERCH South African Site Soweto is a large urban settlement situated 15 kilometres southwest of Johannesburg, in Gauteng Province [455]. Although Soweto is situated in Region D of the City of Johannesburg, the health systems infrastructure of the township caters for the needs of persons resident in parts of Region G as well. Regions D and the parts of Region G draining to CHBAH therefore constituted the study catchment area (Appendix C). Population estimates indicate that 1.8 million people, predominantly black Africans, were resident in Regions D and G from 2011 to 2013, including approximately 160 000 children <5 years of age [456]. Country-wide health care utilisation surveys conducted in 2003 and 2008 indicated that 89% to 95% of South Africans did not have access to medical insurance [457, 458]. At the time of PERCH study enrolment, CHBAH was the only public hospital catering for hospitalisation in Soweto. According to Census 2011 data (Table 2.1), the population density in the study catchment area was 5 208 persons per square kilometre, 64.4% of dwellings were classified as being formal structures, 95.4% of households had access to electricity and considerably fewer (41.5%)

had access to piped water [459–474]. **The unemployment rate** **850**

amongst catchment area residents between the ages of 15 and 64 years was 31.6%, and 19.8% of households had no fixed income (Table 2.1). 51 Tab. 2.1: Household Characteristics in Regions D and G of the City of Johannesburg: Census 2011 Data Suburb PERCH Catchment Area Population Population density Households Average household size Formal dwellings (%) Piped water (%) Flush toilet (%) Electricity (%) No income (%) Unemployment (%) Soweto [460] 1 271 628 6 357 355 331 3.4 84.2 55.0 91.6 93.1 18.7 29.0 Lenasia South [461] 37 110 2 655 9 983 3.7 82.8 68.4 68.7 93.6 18.0 26.8 Lawley [462] 33 136 5 439 10 014 3.3 28.0 20.3 20.2 98.1 20.9 33.1 Vlakfontein [463] 27 291 5 894 8 532 3.2 56.4 37.1 97.0 98.3 21.7 33.0 Orange Farm [464] 76 767 6 312 21 029 3.6 80.5 40.4 70.4 99.0 19.0 33.0 Poortjie [465] 11 153 4 591 3 247 3.4 54.6 28.0 25.4 90.2 20.4 34.8 Catchment Area [460–465] 1 457 085 5 208 408 136 3.4 64.4 41.5 62.2 95.4 19.8 31.6 Lakeside [466] 23 503 6 214 7 039 3.3 97.7 85.6 98.8 99.1 18.5 33.7 Stretford [467] 61 141 8 282 16 998 3.6 76.1 49.8 76.2 98.5 18.8 33.7 Drie Ziek [468] 35 622 4 728 10 555 3.3 55.7 36.9 37.3 92.7 25.9 34.4 Zakariyya Park [469] 6 200 3 160 1 348 4.1 99.2 95.8 99.1 99.6 8.4 26.2 Lenasia [470] 89 714 4 424 25 763 3.4 58.8 55.1 55.6 55.9 15.3 29.6 Kanana Park [471] 21 005 3 079 6 978 2.9 23.0 19.3 21.4 67.7 25.8 33.1 Lehae [472] 13 380 3 819 3 903 3.4 98.1 96.2 99.2 97.9 10.8 34.2 Ennerdale [473] 71 815 3 367 19 844 3.6 62.8 52.0 74.8 91.9 16.8 30.8 Tshepisong [474] 53 260 8 117 17 941 3.0 50.2 47.8 57.1 84.4 17.9 29.9 Regions D and G [460–474] 1 832 725 5 096 3.4 67.2 52.5 66.2 90.7 18.5 31.7 City of Johannesburg [459] 4 434 827 2 696 1 434 856 2.8 81.4 64.7 87.1 90.8 16.8 25.0 = included in catchment area; = not included in catchment area; Table produced using the stargazer package in R [66]. 52 2.1.2Clinical Standardisation in PERCH A previous multi-site childhood pneumonia aetiology study (BOSTID) which was conducted in the 1980s [288] was undermined by the fact that there was little standardisation of clinical case definitions, which impacted on the ability to draw conclusions across sites and translate the study findings into other contexts [291]. Standardisation of case definitions, clinical examination, and collection and processing of specimens from participants was a major focus of PERCH, in an attempt to establish a robust evidence base from which to infer the epidemiology of childhood severe and very severe CAP in LMICs [27, 475]. Reinforcement of clinical standardisation across PERCH sites was ensured by having a single, experienced Paediatrician facilitate initial and refresher trainings at each site (https://www.youtube.com/watch?v=xUI7FV1PQck) [476, 477]. On-site clinical standardisation trainings were held at CHBAH prior to study start-up, in April 2011, and again on three occasions during participant enrolment in February 2012, October 2012 and April 2013. During the clinical standardisation training sessions, WHO pneumonia case definitions and how to recognise them clinically were reinforced by means of lectures, video clips, case scenarios and multiple choice questions. Study staff members were trained to recognise lower chest wall indrawing, head nodding, grunting and other pneumonia danger signs. They were also trained how to measure and record vital signs and anthropometric parameters accurately. Vital signs were measured as follows: 1. Respiratory rate was counted over 60 seconds using a UNICEF Respiratory Rate Timer (UNICEF Supply Division, Copenhagen, Denmark), counting an inspiration and the following expiration as one respiratory cycle by observing the movement of the child's chest or abdomen whilst the child was quiet and not feeding. Use of the timer – which marks the seconds by emitting a steady clicking sound over one minute, beeping at 30 seconds and again at 60 seconds – permitted the observer to visualise the child's breathing pattern throughout the 60 seconds of observation, without being distracted by needing to glance at a watch or clock to track time; 2. Axillary temperature was measured in degrees Celsius (◦C) by using digital thermometers; 3. Pulse and oxygen saturations were measured using Bitmos sat 805 saturation monitors with LNCS YI Multisite Reusable Sensors (Bitmos Medizintechnik, Du¨sseldorf, Germany). Anthropometric parameters were measured as follows: 1. Weight (in kilograms), was measured with child undressed and shoes removed (if applicable), using a Seca 874 digital floor scale (Seca, Hamburg, Germany). Children <24 months of age were measured with the mother standing on the scale, selecting the scale's '2 in 1' function and handing the child to the mother, after which the child's weight was displayed on the scale (through digital subtraction of the mother's weight from the mother's and child's combined weights). Children ≥24 months were weighed by asking them to stand on the scale – those too ill to stand were weighed as per the method used in younger children; 2. Length and height (in centimetres) were measured using a 420 Measure All – Portable Meas- uring Board (Stadiometer.com, North Bend, Washington, United States). Lengths of children <24 months of age were measured in supine, recumbent position with the child positioned to gaze straight upwards, with body straight and soles of the feet against the measuring board. Children ≥24 months had standing height measured once correctly positioned, with gaze looking forward, shoulders aligned, hands at the sides and occiput, shoulder blades, buttocks and heels against the board. Those too ill to stand had length measured as per the method used for younger children. 2.1.3PERCH Cases and Case Selection Cases were

children (28 days to 59 months of age) hospitalised at CHBAH **with** **531**

clinical features compatible

with a diagnosis of severe or very severe pneumonia as delineated by **the** pre-2012 WHO **pneumonia** **684**

classification system (Table 1.1). Participants enrolled as severe pneumonia cases had a history of cough and/

or difficulty breathing, and the clinical finding of lower chest wall indrawing,

without associated ‘danger signs’.

Children admitted with very severe pneumonia were 472

those

with a history of cough and/ or difficulty breathing 27

which was associated with

at least one of the following ‘danger signs’: 403

decreased

level of consciousness, convulsions, inability to feed, vomiting 565

all feeds, central cyanosis, or head nodding [27]. Very severe pneumonia cases need not have presented with lower chest wall indrawing, as this clinical sign is frequently absent, indicating physical exhaustion, in young children who are reaching a state of impending respiratory collapse. Exclusion criteria for enrolment of cases included: 1. Unwillingness of the

parent or legal guardian to give consent for participation in 514

the study; 2. Previous hospitalisation within 14 days of the current admission date (so as not to include possible nosocomial pneumonia episodes); 3. Enrolment

as a PERCH case within the previous 30 days (so as not to sample the 285

same pneumonia episode twice in any given case) [478]; 4. Resolution of

severe pneumonia signs (lower chest wall indrawing) in children presenting with 797

wheeze, after a bronchodilator challenge [27]. The bronchodilator challenge entailed administration of one nebulised dose of ipratroprium brom- ide (Atrovent®, Adcock Ingram, Midrand, South Africa) combined with fenoterol hydrobromide (Berotec®, Adcock Ingram, Midrand, South Africa) to children <24 months of age, and up to three nebulised doses to older children. Children whose lower chest wall indrawing resolved after the bronchodilator challenge were deemed to have reactive airways disease (RAD) rather than severe pneumonia and were ineligible for enrolment into PERCH. Children with features of severe pneumonia and wheezing whose lower chest wall indrawing persisted despite bronchodilator challenge were considered to have severe pneumonia and

were eligible for enrolment into the study. All children 891

with features of very severe pneumonia and wheezing were eligible for enrolment into PERCH, regardless of their response to bronchodilator challenge, as it was assumed that the

danger signs of very severe pneumonia would be unlikely to 990

resolve in response to bronchodilator therapy alone [27, 478]. Enrolment of cases

at the South African PERCH site commenced on 17 August 2011 and concluded on 31 August 2013. 393

Children were enrolled into the study by research nurses and field workers stationed at the paediatric admissions ward at CHBAH during weekdays, weekends and most public holidays on 598 (80.2%) of the 746 paediatric admission days during the study time period. Hours of screening for enrolment varied by

season and study staff availability, but ranged from 13 to 15 hours daily on weekdays and four to eight hours daily on weekends and public holidays. Once consented into the study, cases were subjected to a standardised vital signs and anthropo- metric assessment by study nurses. Clinical signs of pneumonia severity were also evaluated in standardised manner to accurately assign WHO pneumonia severity categorisation. 2.1.4PERCH Controls and Control Selection

Controls were age **-frequency matched to cases** according to **the following age** categories: one **to** five **months,** six **to** 11 **months, 12 to** 23 **months and 24 to** 59 **months.** 216

Controls were also HIV-infection status matched to cases with the aim of achieving a one-to-one ratio between cases and controls. Community Controls Community control procedures entailed monthly compilation of a randomised list of birth dates representative of the frequency of age groups enrolled as cases at the site in the preceding month. These birth date lists were used to cross check against labour ward nursey logs in order to record the names and addresses of the first ten babies born at CHBAH on the randomly generated birth date. Only the names of babies residing in the study catchment area were eligible for inclusion in this list. These lists of names and contact details were compiled into community control recruitment lists which were used in order to visit the identified children so as to invite them to participate in PERCH as community controls. Field trips to the community were time-intensive and took place on every week day, with a driver and field worker going out into the community to identify the potential community controls and invite them to participate in PERCH. During field trip excursions, the field worker visited the home of the first identified child per birth date. If the child was not at home, had relocated, demised, or the recorded address was inaccurate one of two options was used to source an alternative age-appropriate community control: 1. The field worker moved to the next potential child identified from the birth register log; or, 2. A community-based enrolment strategy, adopted in February 2012 to enhance the efficiency of the process of community control enrolment, could be used to source the next available potential community control. Community-based control recruitment entailed moving systematically from door to door (starting at the household to the left of the failed community control's place of residence) and moving from house-to-house down the street until a household was found where an age-frequency matched eligible potential community control was identified. The maximum time permitted for use of the alternative, community-based recruitment procedure was 30 minutes. If after 30 minutes a suitable alternative community control had not been identified, the field worker and driver moved to the next age-frequency matched child's address as recorded on the community control recruitment register. Identified community controls were screened for eligibility to participate in PERCH, and were deemed appropriate for enrolment if: 1. The child was age-eligible for PERCH; 2. The child had not previously been enrolled

as a PERCH case within the past 30 days; 3. **The** 2

child had not been enrolled as a community control in PERCH in the past 30 days; 4. The child was resident in the catchment area (largely controlled for by the fact that community controls were sourced from the study catchment area); 5. The child was not known to be HIV infected (see below for the HIV-infected control recruitment strategy); 6. The child had no

signs of severe or very severe pneumonia (if this was **the** case, the **child** 51

was referred for assessment at the local clinic); 7. The legal guardian was capable and willing to sign informed

consent for participation of the child in the 517

study. At successful interactions with community control households, caregivers and the identified community control were invited to attend

the Respiratory & Meningeal Pathogens Research Unit (RMPRU) 890
outpatient clinic **at**

CHBAH within 72 hours (or, if there was an intervening long weekend, on the first business day following the long weekend) of the field worker visit. RMPRU clinic times were from 08h00 until 16h00, Monday through Friday, excluding public holidays.

Written informed consent was obtained on **the** day **of the** 828

community control's presentation at the RMPRU outpatient clinic. HIV-infected Controls HIV-infected controls were recruited, with permission, from each of the two Paediatric ART Clinics at CHBAH: Harriet

Shezi Children's Clinic and the Perinatal HIV Research Unit (PHRU) Clinic. Hours of clinic screening for HIV-infected controls were from 08h00 to 12h00 on weekdays, excluding public holidays. Lists of the ages of HIV-infected cases already enrolled into PERCH were compiled and regularly updated, and these were used to source age-frequency matched HIV-infected controls into the study, ideally within two weeks of case enrolment. An HIV-infected ART clinic attendee was enrolled if he/ she met the following criteria: 1. The child was age-eligible for PERCH; 2. The child had not previously been enrolled

as a PERCH case within the past 30 days; 3. **The** **2**

child had not been enrolled as an HIV-infected control in PERCH in the past 30 days; 4. The child was resident in the catchment area; 5. The child

was known to be HIV infected; 6. **The child had** **364**

no

signs of severe or very severe pneumonia (if this was **the** case, the **child** **51**

was referred for assessment at the CHBAH paediatric admissions ward); 7. The legal guardian was capable and willing to sign informed

consent for participation of the child in the study. **The** majority **of** **517**

HIV-infected children attending the two above-mentioned ART clinics at CHBAH were on ART at the time of enrolment into PERCH, and were therefore unlikely to represent the clinical spectrum of HIV disease and degree of immunosuppression

of HIV-infected cases presenting **to the general Paediatric wards** **233**

with severe or very severe pneumonia. **25**

The Actuarial Society of South Africa AIDS and Demographic Model **479**
2008 (ASSA2008) estimates **that**

3.5%

of children<5 **years of age** residing in Soweto **are HIV-infected** **855**

[479], therefore our hospital- based recruitment of well HIV-infected children attending ART outpatient clinics represented a convenience sample of HIV-infected children [478]. 2.1.5Procedures Performed on and Specimens Obtained from Study Participants Routine clinical testing in cases Routine clinical specimens submitted on pneumonia cases by ward clinicians

included full blood count with differential, **C-reactive protein** (CRP), **708**
blood culture and

age-specific HIV tests (see page 67). Children newly diagnosed as being HIV-infected, or those known

to be HIV-infected had **CD4+** T **-lymphocyte and HIV viral load** **401**

(HIVVL) determinations done at the discretion of ward clinicians. Cases suspected of having PTB also had GAs submitted for microscopy of acid-alcohol fast bacilli (AFB), mycobacterial culture and Mtb susceptibility testing

at the discretion of the attending physician. Children suspected **of** **783**

having PTB were also screened using the Mantoux test, which was usually done by ward clinicians on the day of hospitalisation by inoculation of 2TU

(tuberculin units) of purified protein derivative (PPD) RT23 **(Statens Serum** Institut, **Copenhagen, Denmark)** into **the** epidermis of the **volar aspect of the left forearm.** **365**

The diameter of induration elicited by Mantoux tests was recorded by ward clinicians 48 to 72 hours post-inoculation using the ballpoint pen method, with the maximal diameter of induration in the transverse plane being recorded in millimetres. Mantoux reactions were interpreted as being positive if

≥5 mm in diameter in HIV-infected or malnourished **children,** or **≥10 mm in HIV-uninfected children** **401**

with normal nutritional status [480]. Chest imaging of cases Children with pneumonia were routinely investigated by obtaining chest radiographs, which were converted from plain film to digital format using an EPSON Expression 10000XL scanner (Seiko Epson Corporation, Suwa, Nagano, Japan). Radiographs were scanned to digital format by the PERCH research team as soon as films became available, and at the end of each month digitised chest radiograph images were uploaded onto a study-specific Dropbox™ folder and archived for interpretation by the PERCH chest radiograph reading panel [481, 482]. Interpretation of chest radiographs was done through submission of digitised images to two members of the reading panel – neither of whom were affiliated with the site at which the film to be interpreted had been obtained. This approach guarded against potential recall bias of site clinicians interpreting films of study participants that had been under their care. The WHO standardised paediatric chest radiograph interpretation scheme [483] was used to interpret each chest radiograph as being: 1. 'Primary end point' – lobar or segmental consolidation with or without air bronchograms and/ or pleural effusion; 2. 'Other infiltrates' – streaky, non-specific changes not coalescent enough to be termed 'consol- idation'; 3. 'Primary end point and other infiltrate' – if features of consolidation and non-specific streaky infiltrates were present; 4. Normal – clear lung fields with no pathologic air space disease; 5. Uninterpretable – film interpreted to be of too low quality to make an informed pronouncement on the presence or absence of pathological changes. In instances where the two readers did not agree on the interpretation of a specific chest radiograph, the image was reviewed by a panel of expert arbitrators (blinded to the results of the initial reading panel interpretations); if the arbitrators disagreed on interpretation of the film, they arrived at a final attribution through discussion and consensus (which took into consideration the interpretations of the initial reading panel and the arbitrators' initial assessments) [481]. A three-tier classification of chest radiograph findings ('abnormal', 'normal' and 'uninterpretable') was developed by pooling 'primary end point', 'other infiltrate' and 'primary end point with other infiltrate' films into a single category – 'abnormal chest radiograph' – and the three-tier classification was used in analyses within this thesis. Study-specific procedures: Cases Study-specific procedures in cases included history taking, with data pertaining to pneumonia risk factors, the child's current illness, and past medical history being captured onto paper-based case report forms (CRFs). Children were examined by ward clinicians, and study nurses – who were not specifically trained to elicit clinical signs such as chest auscultatory findings – transcribed clinical findings from admission notes into CRFs. Study nurses were trained to recognise the signs of severe and very severe pneumonia, and classified each pneumonia case accordingly at admission, they also performed standardised anthropometric assessments on all cases. Nasopharyngeal

-oropharyngeal swabs were collected **from** all cases **as soon as possible after** **792**

they had been consented into the study, in order to determine upper respiratory flora using both traditional bacterial culture methods and a real-time multiplex PCR for 33 respiratory pathogens (FastTrack

Diagnostics Respiratory Pathogens 33 (FTDResp **-33); Fast Track Diagnostics, Sliema, Malta).** **65**

These specimens

were transported in cooler boxes **to the** RMPRU **Research Laboratory** at CHBAH **for** **2**

analysis. Three NP/OP swabs were collected from each case as follows, using: 1. A rayon nasopharyngeal swab (Fisher Scientific®, Loughborough, United Kingdom) which was inserted into a vial of

1 mL skim milk-tryptone-glucose-glycerol (STGG) medium **56**

for pneumococcal culture; 2.

A flocked nasopharyngeal swab (flexible minitip, Copan®, 65

Murietta, California, United States), and; 3.

A rayon oropharyngeal swab (Fisher Scientific®, 65

Loughborough, United Kingdom). The flocked nasopharyngeal and rayon oropharyngeal

swabs were pooled **into a 3 mL** vial containing universal **transport medium (Copan®,** 791

Murietta, California, United States), and tested using the FTDResp-33 assay. Induced sputum specimens were obtained, under close monitoring, from cases as soon as possible after enrolment into PERCH, and again 24 to 48 hours later. The second IS specimen was collected in order to optimise the yield of Mtb from pneumonia cases in this high-burdened setting of tuberculosis (TB) [484]. Contraindications to IS collection included: 1. Oxygen saturations

<92% on supplemental oxygen; 2. **Inability to protect** the **airway;** 3. **Severe bronchospasm;** 4. **Seizure within the** past **24 hours;** 420

5. Attending clinician reluctance to have the child subjected to IS specimen collection. Briefly, IS specimens were obtained after the child had been fasting for two to three hours by pre- bronchodilating them with two metered-dose puffs of 100 µg salbutamol (Asthavent®, Medpro Pharmaceutica (Pty) Ltd, Rosen Park, South Africa) using a baby mask and spacer device. Five minutes following the bronchodilator dose, the child was given a nebulised dose of 5 mL sterile hypertonic (5%) saline (Adcock Ingram Critical Care (Pty) Ltd, Aeroton, South Africa) for a minimum of 10 minutes. Gentle chest percussion was done in order to elicit a cough response during and after hypertonic saline nebulisation. Once a cough had been elicited, a sterile closed loop mucus extractor was gently inserted via the nose into the posterior nasopharyngx. Once correctly positioned, wall suction was applied until sputum could be seen filling half the length of the suction catheter at which time wall suction was discontinued and the catheter withdrawn from the nasopharynx. The sputum sample was

flushed into a collection container with **5 mL sterile normal** (0.9%) **saline** 18

and stored in a cooler box for transport to the RMPRU laboratory at CHBAH. Pulse rate and oxygen saturations were monitored continuously throughout the procedure. In instances where children were receiving mechanical ventilation, and therefore could not be subjected to IS specimen collection, two endotracheal tube (ETT) specimens were collected on consecutive days. The first IS or ETT specimen was aliquoted into three samples: one for FTDResp-33 PCR testing (analysed at the RMPRU laboratory), one for routine microscopy, bacterial culture and susceptibility testing

(processed at the CHBAH **National Health Laboratory Service (NHLS)** 30

microbiology laboratory), and one for mycobacterial culture (processed at the NHLS Mycobac- teriology Referral Laboratory, Braamfontein) whereas the second IS or ETT specimen was sent only for mycobacterial culture [484]. A subset of cases presenting with pleural effusions had PF collected for FTDResp-33 testing, routine microbiology and mycobacterial culture. Furthermore, a subset of cases with peripherally- located consolidation on chest radiograph underwent lung aspiration for FTDResp-33 testing, routine microbiology and mycobacterial culture. Whole blood and serum for lytA and CMV PCR, and antibiotic activity, respectively, were collected from all cases at the time of enrolment into PERCH. Cases were assessed at 24 and 48 hours into their hospitalisation in order to evaluate clinical progression/ resolution of their pneumonia status. They were also evaluated on the day of discharge from hospital and were given a follow-up date 30-days post-enrolment in order to determine their vital status post-discharge. Study-specific procedures: Controls As was the procedure in cases, information pertaining to demography, risk factors for pneumonia and prior medical history was obtained from controls and entered onto paper-based CRFs. A brief clinical assessment, which included evaluation of anthropometry, vital signs, and examination for features of respiratory distress or upper respiratory tract infection (RTI) was also done. Controls had blood collected for haemoglobin analysis, age-specific HIV testing (see page 67), CMV and lytA PCR, and serum antibiotic activity. A subset of controls, enriched for potentially having elevated CRP levels by including those with RTI symptoms, had serum analysed for CRP [485]. All controls had NP/OP swabs collected for pneumococcal culture and FTDResp-33 testing (see page 60), and this was the only sample through which a comparison of the microbiological and virological milieu in the respiratory tract could be undertaken between cases and controls. The NP/OP swab therefore served as the critical comparator in order to infer the aetiology of pneumonia in cases. A subset of controls were also enrolled into a TB infection

substudy and had Mantoux testing done on the day of enrolment into PERCH with follow-up after 48 to 72 hours in order to evaluate the Mantoux reaction as per WHO guidelines (see page 59). 2.1.6The Pneumonia Lung Autopsy Needle Study (PLANS) PERCH provided an opportunity to interrogate the aetiology of fatal pneumonia in under-5 children, and South Africa was one of three sites (the others being Mali and Thailand) which participated in a sub-study of needle biopsy minimally-invasive autopsy in PERCH [486]. The study, termed the Pneumonia Lung Autopsy Needle Study (PLANS), was led by Professor Gareth Turner who formulated the protocol. PLANS activities commenced at the South African PERCH site in September 2012, and any child hospitalised with pneumonia at the hospital until 31st December 2013 was considered eligible for enrolment into PLANS. Pneumonia deaths in children not enrolled into PERCH ante-mortem were also considered eligible for PLANS. Once consented into PLANS, the deceased's lungs were sampled using a minimally invasive approach whereby multiple passes through one puncture site in the fourth intercostal space at the midaxillary line on each side of the thorax was used to collect core lung biopsy specimens. Biopsy cores were collected using a 16G Temno™ disposable biopsy gun

(Becton, Dickinson and Company, Franklin Lakes, New Jersey, United States) 276

after sterilising the deceased's skin surface with povidone iodine. Attempts were made to collect lung biopsy specimens as soon as possible after demise of the child. A total of 16 passes, eight from the right, seven from the left, and one from the lung with the greatest radiologic change, were made in sequence as follows: 1. Two cores for routine microbiology (one from each lung), transported in sterile normal saline; 2. Two cores for FTDResp-33 PCR testing (one from each lung), transported in sterile normal saline; 3. Two cores for mycobacterial culture (one from each lung), transported in sterile normal saline; 4. Two cores for 16S RNA analysis (one from each lung), preserved in DNA/ RNA free 10 mmol Tris-EDTA buffer; 5. Two cores for molecular analysis (one from each lung), preserved in RNAlater ® fixative (Thermo Fisher Scientific, Waltham, Massachusetts, United States); 6. Five histology cores (one each from the

right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe), fixed **in** 537

4% phosphate buffered formalin; 7. One core stored in liquid nitrogen (frozen tissue specimen) from the predominantly involved lobe. The sequence of specimen collection was designed to first complete sampling for the tests which required least contamination, proceeding thereafter to those designed not to focus on the microbiological/ virological aspects of the study. The right lung was sampled first in its entirety, using a single multi-use biopsy needle which was discarded at completion of right lung sampling. Thereafter, a new biopsy needle was used to sample the left lung in its entirety. Once collected, the post-mortem lung biopsy specimens were transported to the NHLS and RMPRU laboratories for processing: microbiological, FTDResp-33 PCR and histologic testing were prioritised as a matter of urgency. Biopsy specimens designated for advanced molecular analysis (16S RNA, molecular analysis and frozen section cores) were archived at −70 ◦C at the RMPRU laboratory and subsequently couriered to Oxford University. The families of deceased children that participated in PLANS were interviewed and debriefed at the RMPRU outpatient clinic once microbiologic and histology results were finalised. Results from the microbiological, FTDResp-33 and histological analyses of the core lung biopsy specimens from the South African PLANS cases, who represented 90% (38/42) of all the cases enrolled in PLANS, are presented in this thesis. 2.2Laboratory Procedures 2.2.1NHLS Laboratory Testing Clinical tests done on PERCH participants that were analysed at the NHLS biochemistry, haematology and/ or microbiology laboratories at CHBAH included: CRP, full blood count, blood culture, HIV testing in cases; CRP, haemoglobin and HIV testing in controls; and HIVVL and CD4+ T-lymphocyte counts in HIV-infected participants. Study-specific specimens (ETT/ IS/ LA) for microbiologic and mycobacterial testing were also processed through the NHLS laboratories. Biochemical analyses The COBAS® CRPL3 C-Reactive Protein Gen.3 enhanced immunoturbidimetric assay, performed on a

Roche/Hitachi cobas c 702 analyser **(Roche Diagnostics, Mannheim, Germany),** 966

was used for standardised CRP analysis on cases and a subset of controls at the NHLS CHBAH biochemistry laboratory. Haematological analyses Full blood count and differential in cases, and haemoglobin levels in controls, were determ- ined using Sysmex XE-5000™ coulter counters (Sysmex, Kobe, Japan) at the CHBAH NHLS haematology laboratory. CD4+ T-lymphocyte counts in HIV-infected cases and controls were analysed on a FC 500 MPL flow cytometer (Beckman-Coulter, Indianapolis, Indiana, United States) using the single platform panleucogated method [487]. Newly-diagnosed HIV-infected cases would, by default, have had CD4+ T-lymphocyte counts performed as part of their pre-ART initiation work-up, however cases known to have been HIV-infected and HIV clinic attendees enrolled as controls may not have had CD4+ T-lymphocyte determinations done on the day of PERCH enrolment. In instances where CD4+ T-lymphocyte counts were not done at the time of enrolment into PERCH, results taken within 30 days prior to, or following, the PERCH enrolment date were considered suitable for assignation of immunological status

at the time of enrolment into the study. 952

The WHO immunologic staging system was used in order to attribute immunological status in HIV-infected cases and controls [488]. Microbiologic analyses Blood cultures were collected from cases by ward clinicians as part of routine clinical prac- tice. Blood specimens were inoculated into BacT/Alert® Culture Media

and incubated in BacT/Alert® 3D 71

automated incubators (bioM´erieux, Marcy l'Etoile, France) within 24 hours of specimen collection, for a maximum of five days. Flag positive blood culture specimens

were inoculated onto 5% **blood,** chocolate **and** MacConkey **agar.** 71

Organism identification

and antimicrobial susceptibility testing were **performed according to** standard **methods.** 74

Isolates considered to be contaminants (as defined by a predefined directory) included: Bacillus spp., Corynebacterium spp., Micrococcus spp., Propionobacterium spp., coagulase-negative staphyl- ococci and viridans streptococci. Specimens that were alarm positive, Gram stain negative and subculture negative

were tested for the presence of pneumococcal **antigen using the** 770

Alere BinaxNOW® S. pneumoniae test (Alere, Orlando, Florida, United States). Induced sputum specimens were processed within two, and not more than 24 hours, post- collection. The quality of IS specimens was evaluated by staining the most purulent portion with Gram's stain: specimens with

<10 squamous epithelial cells per low power field (LPF) **were deemed** 11

to be of high quality [489]. Endotracheal tube, LA, PF and macerated post-mortem lung biopsy specimens were also processed

as soon as possible after collection, **and no later than** 24 **hours** 374

thereafter. Culture of these specimens was done by inoculating blood, chocolate and MacConkey agar plates using a standardised streaking method in four zones. Organisms classed as belonging to the normal oropharyngeal flora included: anaerobes, Capnocytophaga spp., Corynebacterium spp., enterococci, commensal Neisseria spp., coagulase-negative staphylococci, viridans streptococci and yeasts. Specimens culturing organisms not considered as being part of the normal oropharyngeal flora were quantified based on their growth distribution in the zones of streaking,

identified, and underwent **antimicrobial susceptibility testing according to** standard **methods.** 74

Routine microbiological culture of IS specimens has been shown not to contribute to the attribution of pneumonia case status in the pooled analysis of high-quality IS specimens from the PERCH study, as organism prevalence in these specimens was equivalent in the comparison between cases with radiologically-confirmed pneumonia and 'non-pneumonia' cases [257]. 'Non-pneumonia' cases in that analysis consisted of PERCH cases with a normal chest radiograph,

negative blood cultures, normal respiratory rate or non-hypoxic **(in the absence of crackles), or normal respiratory rate and** 344

non-hypoxic (if crackles were heard on chest auscultation) [257]. Endotracheal tube, GA, IS, LA and PF specimens submitted for mycobacterial culture were processed at the NHLS Mycobacterial Referral Laboratory (Braamfontein, Johannesburg)

by decontamination and digestion with sodium hydroxide/ N-acetyl-cysteine 2

according to current guidelines [490]. Fluorescent microscopy of a portion of the resuspended specimen was done to evaluate the specimen for the presence of bacilli staining fluorescent green in the presence of auramine O stain. The remaining material was inoculated into Mycobacterial Growth Indicator Tubes (MGITs) primed with

PANTA™ (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, azlocillin) and incubated for a 276

maximum of 42 days in a BACTEC™ MGIT 960™ instrument

(Becton, Dickinson and Company, Franklin Lakes, New Jersey, United States). 276

Positive cultures were examined microscopically with Ziehl-Neelsen stain and were processed further if AFBs were visualised,

using the HAIN GenoType MtbDRplus assay (HAIN Lifescience, Nehren, Germany) 71

for speciation, and susceptibility testing to isoniazid and rifampicin. Flag- positive MGIT specimens which cultured contaminants were not processed further. Endotracheal tube, IS, LA and PF specimens were subjected to immunofluorescent microscopy using the Light Diagnostics™ Pneumocystis carinii DFA Kit (EMD Millipore Corporation, Temecula, California, United States), in order to detect P. jirovecii cysts. Determination of HIV status in Cases and Controls CHBAH Paediatric Department policy is to ascertain HIV status in all children requiring hospitalisation, and this is routinely done after obtaining verbal consent from a patient's legal guardian. In PERCH, community controls were also tested, with consent, in order to determine their HIV status. HIV serologic

tests (enzyme-linked immunosorbent assay (ELISA) or rapid 869

antibody tests) were done in children with no known history of in utero HIV exposure, as well as in HIV-exposed children that were ≥18 months of age. HIV ELISA assays used at the CHBAH NHLS include the COBAS®

Elecsys HIV combi PT 4th generation assay (Roche Diagnostics, Mannheim, Germany) 463

for initial screening and the

Architect HIV Ag/Ab Combo (Abbott, Wiesbaden, Germany) 868

for confirmatory testing. Rapid HIV tests used included the

Alere Determine™ HIV-1/2 Ag/Ab Combo assay (Orgenics Ltd., Yavne, Israel) and the 463

Hexagon HIV 3rd generation assay (HUMAN Gesellschaft fu¨r Biochemica und Diagnostica, Wiesbaden, Germany). Nucleic acid testing for HIV was done in all children

<18 months of age that had a positive antenatal HIV exposure history, or 777

for children <18 months of age with a positive serologic 750

result. The

Roche COBAS® AmpliScreen HIV-1 Test, version 1.5 was used 743

for HIV PCR testing, and the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 659

Test version 2 was used to quantify HIVVL (both

Roche Molecular Systems, Inc., Branchburg, New Jersey, United States). 930

Histopathologic analyses Post-mortem lung biopsy specimens were processed using standard histopathological procedures at the CHBAH NHLS histopathology laboratory. Tissue was preserved in

formalin fixed paraffin embedded blocks and cut into 4 µm sections 736

for histochemical staining. Haematoxylin and eosin was the initial stain used. Other staining methods (Grocott silver, Alcian Blue/ Periodic Acid-Schiff (PAS), PAS diastase, Wade Fite, Ziehl-Neelsen and immunohistochemistry for CMV) were used at the discretion of the histopathologist who was interpreting the slides, based on histological appearance of the haematoxylin and eosin-stained tissues. Digital photographs of pertinent pathologic change in each PLANS case were captured using a Zeiss Axiocam ERc5s Color Microscope Camera (Carl Zeiss AG, Oberkochen, Germany). 2.2.2RMPRU Laboratory Testing FTDResp-33 PCR of respiratory specimens & post-mortem lung biopsies The FTDResp-33 PCR assay used in PERCH is designed to detect the following pathogens: • Bacteria: B. pertussis, C. pneumoniae, H. influenzae type b, non-type b

H. influenzae , K. pneumoniae , Legionella spp., M. catarrhalis, M. 801

pneumoniae, Salmonella spp., S. aureus and S. pneumoniae ; • Fungal species: P. jirovecii ; • Viruses: adenovirus, human bocavirus, CMV,

coronavirus 229E, coronavirus OC43, coronavirus NL63 and coronavirus HKU1, 33

enterovirus, HMPV A, HMPV B, influenza A, influenza B, influenza C,

parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, parechovirus, human rhinovirus, RSV A and RSV B. 33

Total nucleic acid was extracted from respiratory specimens (ETT, IS, LA, NP/OP, PF)

using the NucliSENS® easyMag® system (bioM´erieux, Marcy l'Etoile, France). 781

For post-mortem lung biopsies, fragmented tissue samples were digested with proteinase K prior to undergoing nucleic acid extraction. 400 µL of respiratory specimen or proteinase K-digested tissue sample was eluted to

a final volume of 110 µL nucleic acid. Real-time PCR was performed 722

using an Applied Biosystems 7500 platform (Applied Biosystems, Foster City, California, United States) with cycling conditions set at 50 ◦C for 15 minutes, 95 ◦C for 10 minutes, and 40 cycles of 95 ◦C for eight seconds followed by 60 ◦C for 34 seconds. lytA PCR on blood 182

Total nucleic acid extraction for lytA PCR testing was also done with the NucliSENS® easyMag® system.

74

200 µL of whole blood was eluted to a final volume of 100 µL using the NucliSENS 'Specific B' protocol. Extracted DNA was stored at −70 ◦C and batched for

lytA PCR testing which was done using the United States Centers of Disease Control method using a recently- validated probe [491, 492]. PCR analysis was done using an Applied Biosystems 7500 platform with cycling conditions set

at 95 ◦C for 10 minutes followed by 40 cycles of 95 ◦C for 15 seconds and 60 ◦C for one minute. 56

CMV PCR on blood Archived whole blood from PERCH participants with CMV-positive FTDResp-33 results were prioritised for CMV DNAemia testing using the CMV R-gene™ assay (Argene, Verniolle, France) according to the manufacturer's instructions.

200 µL of whole blood was eluted to a final volume of 100 µL using the NucliSENS 'Specific B' protocol. 74

The Applied Biosystems 7500 platform was used for PCR amplification of the target sequence – human CMV tegument phosphoprotein 65 (UL83) [493, 494] – with cycling conditions set

at 95 ◦C for 15 minutes followed by 45 cycles of 95 ◦C for 10 seconds and 60 ◦C for 40 seconds. 485

Two different CMV genes, encoding unique short glycoproteins 7 and 8 (US7 and US8) [495, 496], constitute the pathogen targets for the FTDResp-33 test which was done on respiratory specimens. Serum antibiotic activity testing Serum specimens collected at enrolment were used to test for antibiotic activity in all PERCH participants, as described by Driscoll et al [497, 498]. 20 µL serum was used to inoculate a 6 mm diameter disc of filter paper,

placed on a Mueller-Hinton plate seeded with a 0.5 McFarland suspension of susceptible Staphylococcus aureus subsp. aureus (ATCC® 25923™) 74

(American Type Culture Collection, Manassas, Virginia, United States). Zones of inhibition were assessed after 18 to 24 hours of incubation: any zone of inhibition around a disc was interpreted as being evidence of serum antibiotic activity. 2.3Study-specific Definitions 2.3.1Assignation of HIV exposure status Study participants were considered to have definite in utero HIV exposure if: 1. Their mothers gave a history of being diagnosed as HIV-infected prior to or during her pregnancy with the child; 2. Serologic tests for HIV in the child were positive and the child was <7 months of age; 3. The child and mother were HIV-infected. Study participants were deemed to be definitely unexposed to HIV in utero if: 1. There was documentation of negative maternal serostatus in the antenatal period, and/ or; 2. Serologic HIV tests were negative in any child <7 months of age; 3. The child was confirmed to be HIV-uninfected and a maternal HIV serologic test done at the time of enrolment into PERCH was negative. HEU status was assigned to any HIV-uninfected child: 1. Whose mother gave a history of having been diagnosed with HIV antenatally, or who had accessed ART in the antenatal period; 2. <18 months of age whose HIV serologic tests were positive but whose nucleic acid tests for HIV were negative. HIV-unexposed status was assigned in children: 1. <7 months of age whose HIV serologic tests were negative; 2. ≥7 months of age whose serologic HIV tests were negative and whose mothers had a negative HIV serologic test at the time of PERCH enrolment; 3. ≥7 months of age whose serologic HIV tests were negative and whose mothers reported being HIV negative during pregnancy (presumably unexposed). HIV-uninfected children <18 months of age with missing HIV serology results and unknown maternal HIV status were deemed to have unknown HIV-exposure status. 2.3.2Other Definitions Certain consensus definitions were derived at by the various Working Groups involved in the study, and are listed here: • Clinical Definitions: – Fever: Either axillary temperature ≥38.8

◦C or fever in the past 48 hours as reported by 18

the care giver; – Hypoxia: Oxygen saturations <90%, or on

supplemental oxygen if a room air oxygen saturation reading was not available; 18

– Tachycardia: >160 beats

per minute for children one to 11 **months of age,**>150 beats **per minute for children** 12 **to** 35 **months of age and**>140 beats **per minute** in **children** 36 **to** 59 months **of age;** **123**

– Tachypnoea:

≥60 breaths per minute in **children**<2 **months of age, ≥50 breaths per minute** in **children** 2 **to 11 months of age and ≥40 breaths per minute for children** 12 **to** 59 months **of age;** **123**

– RTI: Applicable to controls only – the presence of cough, difficulty breathing with fever, ear discharge, runny nose, sore throat, or wheeze if reported by the caregiver, in the absence of

clinical features of WHO-defined **severe or very severe pneumonia.** **861**

• Laboratory-derived Definition: –

Microbiologically-confirmed pneumococcal pneumonia (MCPP): S. pneumoniae identified **by** **105**

culture in a normally sterile site (or by BinaxNOW® on blood culture or PF, or by FTDResp-33 PCR of LA or PF)

in a child hospitalised with **WHO-** defined **severe or very severe pneumonia.** **51**

Normally sterile sites include blood culture, LA and PF. • Meteorological seasons were defined, per convention for the Southern Hemisphere [499], as: – Summer: 1 December to 28 February (29 February in 2012, a leap year); – Autumn:

1 March to 31 May; – Winter: **1 June to 31 August;** – Spring: **1 September to 30 November.** **3**

• Vaccination Status Definitions: – For HibCV: complete vaccination was defined as ≥3 doses; – For PCV:

was defined based on the number of doses of PCV **a child** had **received, and age at first dose or age** (if applicable) **at** PCV **introduction in** **285**

South Africa.

Complete vaccination for PCV was defined as: ∗ ≥3 doses, **or;** ∗ 2 **doses if there was at least 8 weeks between doses and the child was <9 months of age at** enrolment **or >12 months of age at the time of the first dose, or; ∗ ≥1** dose **if the age at any of the doses, or age at introduction, was ≥24 months.** **104**

2.4Statistical Methods 2.4.1Exploratory Statistical Analyses A frequentist approach was applied to the analysis of all work presented in this thesis, and all statistical testing was conducted by the PhD candidate using R statistical software version 3.3.3 [500]. Definitive analysis of pneumonia aetiology in the overarching and site-specific PERCH papers employed a Bayesian approach to analysis of the data, which was not used in the analyses described herein. Continuous variables were summarised in terms of

means and SDs **for normally-distributed data, and medians** and **interquartile ranges** (IQRs) **for skewed data.** Categorical **data** **607**

were summarised in terms of percentages, and proportions. Continuous and categorical variables were compared between groups using logistic regression (using the glm function in R), correcting for age (in months) and season. In analyses which entailed multiple comparisons, and which may therefore by chance have given rise to seemingly significant statistical outputs, P-values were adjusted using the Benjamini-Hochberg procedure [501]. 2.4.2Organism Density Cut-offs The quantitative FTDResp-33 PCR assay used in this study gave rise to estimates of pathogen density (expressed in cycle threshold (Ct) values), which were transformed into decimal logarithm (log10) pathogen copies/mL

using 10-fold serial dilutions of plasmid standards which were supplied **by** 65

the manufacturers of the assay [502]. This, site-specific assay standardisation procedure was conducted 3-monthly during conduct of the study [502]. Receiver operating characteristic (ROC) curves were generated for the South African site pathogen densities in order to determine the optimal pathogen density that distinguished between case and control status, using the Youden index [503]. As the Youden index tends to over-estimate the accuracy of diagnostic tests when applied to studies with a small sample size (n<200) [504],

leave-one-out cross validation was used to 851

derive a more conservative Youden cut-off for each pathogen under interrogation [502]. Analyses were restricted only to children in whom the PCR target pathogen was detected in NP/OP or whole blood specimens [505]. These ROC analyses were conducted for the South African PERCH cohort as a whole, using cases with radiologically-confirmed pneumonia as the main comparator group. ROC analyses were done for all children, and

stratified by HIV infection and -exposure status 602

(HIV-uninfected, HEU, HIV-unexposed, HIV-uninfected with unknown exposure status and HIV-infected). Where sample sizes were too small to derive a suitable cut-off density, the cut-off density derived for a larger group (HIV-uninfected for HEU, HIV-unexposed and HIV-exposure status unknown children; the entire South African PERCH cohort for HIV-infected children) was used as a proxy for the sub-group pathogen-specific density cut-off. Application of cut-off density thresholds to the study cohort Only certain density cut-offs were applied to the cohort once cut-off density thresholds for the pathogens tested in the FTDResp-33 PCR and whole blood lytA and CMV assays had been derived. The rationale for not applying all cut-off densities to the cohort was based on observations which evaluate the utility of modern molecular methods in childhood pneumonia diagnostics [502, 506–508], and has been summarised in Figure 2.1. Briefly, these studies reported that the presence of certain organisms detected on upper respiratory tract specimens by molecular methods may fall into one of two camps: Always considered pathogenic if detected on NP/OP swabs: no need for a cut-off density FLUA, FLUB, FLUC, HMPV, PARA1, PARA2, PARA3, PARA4, RSV, BOPE, CPNEU, MPNEU [506, 507] NP/OP and WB PCR Data No density threshold adjustment in view of small numbers of cases positive and/ or predominance in controls: COR43, COR63, COR229, CORHKU, PV/EV, SASP Prevalence data for: 1. Entire cohort 2. HIV-uninfected • HEU • HIV-unexposed • HIV exposure unknown 3. HIV-infected Density thresholds using ROC analysis and Youden index with leave-one-out cross-validation Resort to use of cut-off density as may present colonisation status: ADENO, CMV, HBOV, RHINO, HIB, HINF, MCAT, PNEU, SAUR, PJP [502, 508] 2. Methods 74 Fig. 2.1: Choice of Density Cut-off Thresholds for Organisms Detected by PCR of NP/OP and Whole Blood Specimens – South African Site ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus; HEU = HIV- exposed, -uninfected;

HIB = H. influenzae type b; HINF = non **-type** b **H. influenzae** 36

; HIV =

human immunodeficiency virus type 1; HMPV = human metapneumovirus; 121

MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = parainfluenza virus type 2; PARA3 = parainfluenza virus type 3; PARA4 = parainfluenza virus type 4; 20

PCR = polymerase chain reaction; PJP = P. jirovecii ; PNEU = S. pneumoniae 32

; PV/EV = parechovirus/ enterovirus; RHINO = human rhinovirus; ROC = receiver operating characteristic;

RSV = respiratory syncytial virus; SASP = Salmonella spp.; SAUR = S. aureus ; WB = whole blood. 1. 534

Colonisers that (in high density) may represent aetiologic agents in pneumonia cases, or 2. Firmly-established pathogens that if detected are likely associated with

lower respiratory tract illness in symptomatic cases. The first group of 362

organisms would need to have a cut-off density threshold applied to them in order to attribute case status in a case-control analysis, whilst the second group need not have a threshold applied because the presence of the organism – regardless of density – suggests a high probability for causality of LRTI. Organisms that may represent colonisers and require a cut-off density threshold to be applied include adenovirus, CMV, human bocavirus, human rhinovirus, H. influenzae (type b and non-type b), M. catarrhalis, S. pneumoniae, S. aureus and P. jirovecii [502, 508]. Organisms almost invariably associated with disease include HMPV, influenza and parainfluenza viruses, RSV, and atypical pathogens B. pertussis, C. pneumoniae and M. pneumoniae [506, 507]. In this analysis, if few cases and controls were positive for a group of pathogens, or the pathogen in question was more frequently detected in controls, limiting the utility of the study to draw conclusions about their role in pneumonia pathogenesis, the case-control analysis was done using unadjusted prevalence of the organism (i.e. no cut-off density was applied). This situation arose for the coronaviruses, parechovirus/ enterovirus and Salmonella spp. in this analysis (Figure 2.1). Issues regarding PCR testing for Klebsiella pneumoniae and Legionella spp. in NP/OP swabs, and CMV in whole blood specimens Not all pathogens tested for in the FTDResp-33 assay were included in the analysis of pneumonia aetiology in the PERCH analyses. Problems with assay specificity for K. pneumoniae and Legionella spp. necessitated their exclusion from the analyses [250, 295]. However, in the analysis of PLANS data, FTDResp-33 PCR K. pneumoniae results were retained for comparison against culture-positive specimens, as K. pneumoniae featured prominently amongst the bacterial isolates cultured in cases dying from pneumonia and enrolled into PLANS. CMV whole blood PCR testing was done only in the subset of study participants at the South African site that had PCR evidence of disease associated with CMV on testing of NP/OP swabs and IS specimens, as it was assumed that children testing negative for CMV on NP/OP swabs and IS specimens would be negative for CMV on whole blood testing. This assumed prevalence rate is likely to give rise to a conservative estimate of the role of CMV whole blood PCR positivity in childhood pneumonia cases at the South African PERCH site, as other studies have demonstrated the presence of CMV DNAemia in asymptomatic African infants [509, 510]. 2.4.3Case Control Analysis: Organism Fractions of Association with Case Status, Using NP/OP Swabs as the Reference Sample Odds ratios were derived using marginal and conditional logistic regression by correcting for age (in months) and season. In conditional analyses, statistical outputs were further controlled by adjusting for all other pathogens (other than the pathogen under investigation in each analysis). This analytic approach permitted comparison of NP/OP swab and whole blood organism profiles between cases and controls, overall and stratified by different parameters (see page 77). Bruzzi et al [454] noted that the attributable fraction (AF),

i.e. the proportion of disease attributed to 965

a specific aetiologic factor at a population level which could be prevented if the aetiologic factor in question was eliminated from the population, may be estimated using a case control approach which adopts conditional logistic regression in order to derive the odds ratio. The AF approach has been used in other aetiologic studies of paediatric illness, notably in the GABRIEL study of childhood pneumonia mentioned above (see Section 1.4.3) and the Global Enteric Multicenter Study (GEMS) [289, 511, 512]. In both GABRIEL and GEMS, AF was defined as: AF = (P | cas) × (1 − 1/OR) (2.1) where P | cas represents the proportion of cases positive for an aetiologic agent using a diagnostic assay and OR is the odds ratio, derived using conditional logistic regression. The AF is typically derived in instances in which the lower bound of the odds ratio's 95% CI exceeds 1, i.e. where detection of the aetiologic agent is significantly

associated with case status, and is (usually) expressed as a proportion (not as a percentage). For the current analysis, where NP/OP swab results were used as a proxy marker of association with pneumonia hospitalisation through the case control analysis, it would be incorrect to call the fraction of pneumonia ascribed to the detection of an organism on NP/OP swabs an 'attributable fraction'. Rather, we have chosen to describe our results as 'fractions of association' (FA) so as to draw a distinction between our use of a proxy measure of disease aetiology (upper respiratory tract organism prevalence in cases compared to controls) and the ideal scenario in which specimens derived directly from the lung would be highly representative of the actual cause of the pneumonia. Therefore, for the purposes of this analysis: FA = (P | casN P /OP) × (1 − 1/ORcas) (2.2) where FA is the 'fraction of association', P | casN P /OP represents the proportion of case NP/OP swabs positive for a particular organism or group of organisms, and ORcas represents the odds ratio derived by using the cases as the group of interest. For lytA and CMV on whole blood (WB) specimens, the FA equation substituted 'NP/OP' with 'WB' to reflect the appropriate specimen tested, as follows: FA = (P | casW B) × (1 − 1/ORcas) (2.3) Method of FA analysis Case and control FTDResp-33 results from NP/OP swabs, and whole blood PCR results (for lytA and whole blood CMV) were compared in this analysis, overall and stratified by HIV-infection and -exposure status according to: • Radiologically-confirmed disease; • Age group (one to 11 months, 12 to 59 months); • Pneumonia severity; • In-hospital mortality. Cases consisted only of the subset of South African PERCH cases with radiologically-defined pneumonia. 2.4.4Pneumonia Incidence Calculations Pneumonia incidence calculations were made using the aetiology-specific pneumonia attribution estimates observed through the case-control analysis conducted above, adjusted by taking into account the unsampled pneumonia cases admitted to CHBAH during the study time-period; this served as the numerator for aetiology-specific incidence rate calculations. The CHBAH Paediatric Admission and Discharge Registry

was used to determine the total number of **238**

PERCH age-eligible pneumonia cases hospitalised in the general paediatric wards during the study time frame, and their HIV infection status. Assumptions made with regards the numerator values included: 1. Where the age of children hospitalised in the CHBAH general paediatric wards was unknown in the Paediatric Admission and Discharge Registry (n=158), it was assumed that they fell in equal proportion amongst the four age categories (one to five months, six to 11

months, 12 to 23 **months and 24 to** 59 **months)** **846**

as did those with known age; 2. With regards missing HIV infection status in the CHBAH Paediatric Admission and Discharge Registry (n=1 814), it was assumed that those with undetermined HIV infection status had the same propensity to be HIV-infected or -uninfected as did those with known HIV status; 3. With regards the PERCH cases that had undetermined HIV exposure status (n=42), these children were apportioned as being either 'HIV-unexposed' or 'HEU' based on the proportional split of HIV-unexposure and HEU within each age category thereby deriving a 'refined HIV exposure status' parameter; 4. After deriving a 'refined HIV exposure status' parameter, it was

assumed that the proportion of children diagnosed as having **pneumonia and** **881**

that were HEU was similar to that observed in the PERCH cohort. HIV-unexposed children were simply assigned as being the number of HIV-uninfected children minus the number of HEU children. Numerator data, for the cohort as a whole and stratified by study year (with children hospitalised during the first year of the study being defined as those cases hospitalised between 17th August 2011 and 16th August 2012, and those hospitalised between 17th August 2012 and 31st August 2013 comprising the cohort hospitalised during the second year of the study) are shown in Appendix D. Denominators (Table 2.2) were derived from City of Johannesburg Region D and portions of Tab. 2.2: Denominators Used for Incidence Rate Calculations in the PERCH Catchment Area Age Group Estimate Total Population Number In Each Age Under-5 Proportion of HIV+b HIV- HEUc HIV- unexposedd Cross- referencee in Group Total Catchment Areaa Population (%) <1 yearf Lower 1 457 085 14 764 517 14 248 3 853 10 394 Middle 1 457 085 23 328 816 22 512 6 089 16 423 Upper 1 745 515 32 659 1 143 31 516 8 524 22 992 ≥1 &<2 yearf Lower 1 457 085 14 782 517 14 265 3 858 10 407 Middle 1 457 085 23 357 817 22 539 6 096 16 443 Upper 1 745 515 32 699 1 144 31 555 8 534 23 020 ≥2 &<5 yearf Lower 1 457 085 44 488 1 557 42 931 11 611 31 320 Middle 1 457 085 70 293 2 460 67 833 18 346 49 486 Upper 1 745 515 98 409 3 444 94 965 25 685 69 280 Under-5 Lower 1 457 085 74 035 5.1 2 591 71 444 19 323 52 121 Table E.4 Middle 1 457 085 116 978 8.0 4 094 112 884 30 531 82 353 Table E.5 Upper 1 745 515 163 767 9.4 5 732 158 035 42 743 115 292 Table E.3 a PERCH catchment area defined as the area in which 90% of age-eligible paediatric admissions to the study hospital resided in the year prior to PERCH activities in Soweto (see Appendix C) – for the lower and middle population estimates, the estimate is further refined through being derived from the Census 2011 data which offer population estimates to sub-district level (see Appendix E); b In 2012, 3.5% of under-5 children in Gauteng Province were estimated to be HIV-infected (Table E.1); c Number of HEU children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), minus the number of HIV-infected children; d Number of HIV-unexposed children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), subtracted from the total

number of under-5 children in the catchment area; e Please refer to the Tables cross-referenced and Appendix E for the rationale by which these denominators were derived; f The <1 year, ≥1 &<2 year, and ≥2 &<5 year age groups are distributed in proportions of 0.19942 (i.e., 32 659), 0.19967 (i.e., 32 699) and 0.60091 (i.e., 98 409) within the total under-5 age group (see Table E.3); HEU = HIV-exposed, 163 767 163 767 163 767 2. Methods 79-uninfected; HIV+ = HIV-infected; HIV- = HIV-uninfected. Region G population estimates [456, 459–474], adjusted for the fact that 90% of the catchment region population was included in the study catchment area (Appendices C and E).

Estimates of HIV- infection **prevalence in the population** at large **were** **107**

derived from the ASSA2008 Model [479]. Denominators for HIV-exposed children were derived by multiplying the under-5 population in the City of Johannesburg by the antenatal HIV seroprevalence (29.6% in 2012, [326]). Lower, mid- and upper estimates of the under-5 childhood population residing in the PERCH catchment area, with stratification by HIV infection and -exposure status, are tabulated in Table 2.2, with the rationale for derivation of these figures explained in Appendix E. The middle population estimate was for the definitive – and pathogen-specific – incidence rate analysis, as the total number of under-5 children (n=116 978) closely mirrored 90% of the estimated 120 000 under-5 children resident in Soweto from previous studies [242]. Derivation of pathogen-specific incidence rates The method by which pathogen-specific incidence rates were derived was to multiply the group- specific summary incidence rate by the FA (if available) for each pathogen. The equation: I n = 100 000 × N (2.4) where n is the numerator, N the denominator and I is the incidence rate – a simple reworking of the basic incidence rate calculation (where incidence is expressed in terms of

number of cases per 100 000 population) – n **I** **170**

= N × 100 000(2.5) was used to derive the pathogen-specific numerators. Once these numerators had been calculated, numerator and denominator data were used to derive the relative risk of disease attributed to each pathogen, comparing the incidence rates

in HIV-infected children **to HIV-uninfected children and** HEU children to **HIV-** unexposed **children.** **345**

2.4.5 Evaluation of the Diagnostic Yield of IS and GA Specimens

for the Diagnosis of PTB **in Children** Hospitalised **with Acute Pneumonia** **2**

South Africa was the only PERCH site that routinely submitted two IS specimens for Mtb culture, and so presented a valuable opportunity through which to investigate the additional diagnostic yield of IS, and GA in establishing a microbiologic diagnosis of disease caused by Mtb. Other PERCH sites would need to consider adjusting their prevalence of pneumonia attributed to Mtb in light of the additional diagnostic yield findings from the South African site. In order to determine the diagnostic yield of IS and GA for the diagnosis of culture-confirmed PTB in the context of acute CAP in children, seven head-to-head comparisons of the numbers of cases with specimens positive for Mtb were conducted as follows: 1. Comparison of the yield of the first versus the second IS specimen; 2. Comparison of the yield of one IS to one GA; 3. Comparison of the yield of one IS to two GA specimens; 4. Comparison of the yield of one IS to three GA specimens; 5. Comparison of the yield of two IS specimens to one GA; 6. Comparison of the yield of two IS specimens to two GA specimens; 7. Comparison of the yield of two IS specimens to three GA specimens.

McNemar's $\chi 2$ **test was used to** determine **the** degree **of** concordance between **the** **365**

samples evaluated in each comparison. 2.4.6Assignation of Infectious Aetiology in PLANS Cases The following approach was used to assign a possible aetiologic diagnosis for children dying from pneumonia and included in the PLANS study, with strength of the assignation being graded as 'strong', 'moderate' or 'weak': • Strong evidence for pathogen attribution to fatal pneumonia was assigned in: – Cases with organism observed on post-mortem lung biopsy specimens, and FTDResp-33 PCR of lung biopsy tissue positive for that organism; – Cases dying within 96 hours of hospitalisation whose blood culture and lung biopsy FTDResp-33 PCR results were concordant; – Cases sampled <24 hours of death, with pure growth of a bacterial organism on post- mortem lung biopsy culture; • Moderate evidence for pathogen attribution to fatal pneumonia was assigned in: – Cases with organism observed on post-mortem lung biopsy specimens, but whose FTDResp- 33 PCR was not completely concordant with the histologic evidence; – Cases dying within 96 hours of hospitalisation whose blood culture and lung biopsy FTDResp-33 PCR results were not concordant; – Cases sampled ≥24 hours and <36 after death, with pure growth of a bacterial organism on post-mortem lung biopsy culture; – Cases with pure identification of viral pathogens on NP/OP and/ or lung biopsy specimen PCR testing; – Cases whose blood and lung biopsy cultures were concordant, regardless

of time frame to post-mortem biopsy; – Cases culturing a significant isolate on blood culture with or without culturing that organism on post-mortem lung biopsy, regardless of time frame between death and post-mortem biopsy sampling; • Weak evidence for pathogen attribution was assigned in: – Cases sampled ≥36 hours post-mortem whose lung tissue cultured a pure growth of a bacterial pathogen; • No assignation of infectious cause of death could be made in children whose battery of tests were negative for any pathogen, or whose lung biopsy FTDResp-33 PCR test was positive for more than one potential pathogen but without other evidence to support which of the detected pathogens was responsible for the pneumonia episode. 2.4.7Evaluation of CMV Whole Blood PCR in Paediatric Pneumonia Cases A subset of PERCH participants at the South African site had blood submitted for CMV whole blood testing; the group of children prioritised for such testing was those who were CMV PCR positive on FTDResp-33 testing of respiratory secretions, with the assumption that those testing negative for the organism on PCR testing of respiratory secretions would be unlikely to have CMV detected on whole blood PCR at densities greater to the cut-off density which best distinguished between cases and controls. The cut-off density for CMV on whole blood was derived by stratifying the cohort according to HIV-infection and -exposure status, and through leave-one-out cross validation in ROC analysis of the densities as per the strategy which was adopted in deriving the cut-off densities for all other pathogens tested for on FTDResp-33 of NP/OP swabs and lytA on whole blood (see Section 2.4.2). Children negative for CMV on NP/OP swab FTDResp-33 testing were arbitrarily assigned a negative result for CMV whole blood density greater than or equal to the HIV-infection and/ or -exposure status specific cut-off. Using leave-one-out cross-validation in ROC analysis of CMV densities on NP/OP and whole blood CMV PCRs made it possible to derive a further sub-group of children: those positive for CMV at greater than cut-off density on both NP/OP swabs and whole blood. For direct comparison between cases and controls, only children with available NP/OP CMV PCR results were evaluated in terms of their CMV whole blood results. A clinical severity composite variable was derived, in order to compare cases with severe and non-severe disease. Severe disease, according to this composite measure was assigned to cases that: • Underwent mechanical ventilation; or, • Had a duration of hospitalisation >5 days; or, • Died at any time during the course of their PERCH hospitalisation episode. Furthermore, in order to qualify as having severe disease according to the severity composite measure, cases needed to have radiologically-confirmed pneumonia. The clinical and laboratory characteristics of cases with and without severe disease were compared against controls using conditional logistic regression controlling for age (in months). Additionally, in order to enrich the 'severe composite' cases for possible CMV-associated pneumonia, ROC analysis with leave-one-out cross validation to describe the Youden index cut-off density of CMV on FTDResp-33 PCR amongst cases with 'severe composite' disease were obtained. Cases with 'severe composite' disease and CMV NP/OP densities greater than or equal to this Youden index were ascribed as being likely to have CMV-associated pneumonia. The performance of CMV whole blood PCR was evaluated in three groups, using conditional logistic regression corrected for age (in months), season and all other pathogens (as detected on FTDResp-33 PCR of NP/OP specimens) in the final analysis: cases likely to have CMV-associated pneumonia, cases unlikely to have CMV-associated pneumonia, and controls. The FA for pneumonia associated with CMV detected on whole blood were derived by using Equation (2.3). CMV viral loads on respiratory specimens and whole blood were not standardised against the WHO Reference Strain so as to achieve cut-off densities that would be transferrable from the context of the current study to other sites [513–515]; hence recommendations cannot be made from this analysis regarding what (standardised) cut-off levels best predict an aetiologic diagnosis of CMV pneumonia. Neither the FTDResp-33 nor the R-gene™ CMV assays had incorporated the reference standard into their methodologies at the time of study conduct. 2.5Role Played by the PhD Candidate in the PERCH Project The PhD candidate was the lead clinician on the PERCH study from its inception in July 2011

at the South African site. The PhD candidate **was** involved **in** **958**

preliminary PERCH meetings, at which site set-up for readiness to participate in the study was discussed and study procedures were being formulated, the first at Muldersdrift (Johannesburg) in September 2010, and the second in Bangkok (Thailand) in May 2011. He was designated to be the clinical lead on PERCH at the South African site by the site's principal investigator and his PhD supervisor, Professor Shabir Madhi, in April 2011 and worked full-time on PERCH from July 2011 until September 2014. He

contributed to the development of study CRFs, **and** refined these with **the** **916**

assistance of the PERCH Core Team, to capture more accurately data fields relevant to the South African PERCH site. He also participated in monthly Clinical Working Group conference calls with the PERCH Core Team which were held across-sites in order to refine clinical aspects of the study and report on progress in the study during its enrolment period. He contributed substantially to the case definitions of HIV exposure status for PERCH, as well as determining the clinical relevance of Mtb in the culture-confirmed tuberculosis cohort for which a sub-committee was set up to evaluate whether Mtb was a cause or a risk factor for the PERCH pneumonia episode. On an average weekday during study conduct, the PhD candidate reviewed and updated the log book of

cases and controls enrolled in the study, focussing **on** **841**

children enrolled into the study over the preceding two to three days in whom most of the study activity was focussed. He assisted with the collection of IS specimens on critically ill children, liaised with the NHLS at CHBAH in order to expedite specimen processing, and co-ordinated the activities of study nurses, research assistants and field workers. He also liaised with clinicians in the general paediatric wards and ICUs at the study hospital (and outlying facilities, where a few of the study children requiring ventilation had been referred for management if no ICU bed was available at the study hospital) relaying the results of FTDResp-33 results to them. The PhD candidate scanned plain film chest radiographs into digital format on a daily basis for electronic archiving, and kept an electronic database on the completeness of the case chest radiograph archive. He uploaded the accumulated digitised chest radiograph images onto Dropbox™ for capture into the centralised PERCH database on a monthly basis. The PhD candidate was a member of the PERCH chest radiograph reading panel, having participated in two training sessions dedicated to familiarising clinicians in the WHO

standardised interpretation of paediatric chest radiographs [483]. **The** first **of** **19**

these training sessions – convened by the Hib Initiative and chaired by Dr Kim Mulholland – was held in Hanoi (Vietnam) on the 11th and 12th October 2011, and the second – convened by the PERCH Core Team – was held in London (United Kingdom) from 27th to 30th August 2012. From end-September 2012, when ethics permissions were granted for participation of the South African PERCH site in the PLANS sub-study, the PhD candidate recruited cases of children dying of pneumonia-related illness into the PLANS study. He liaised with the CHBAH mortuary on a daily basis in order to detect PERCH age-eligible children that had demised in the general paediatric wards or ICU and contacted family members of the deceased in order to ascertain whether they would be amenable to participating in PLANS. If a family consented to participation in the PLANS study, the PhD candidate, a study nurse and a research assistant visited the mortuary in order to collect specimens relevant to PLANS from the subject that had been consented into the study. He couriered all post-mortem specimens to the CHBAH NHLS receiving office, and the RMPRU research laboratory, in order to ensure that all specimens were processed expeditiously. The PhD candidate corresponded regularly with the hospital-, university- and international collaborator-based ethics committees in order to ensure that the study ethics approvals were up- to-date. He was instrumental in drafting Materials Transfer Agreements (MTAs) for transport of Mtb isolates from the NHLS Mycobacteriology Referral Laboratory (Braamfontein, Johannesburg) for archiving at the RMPRU research laboratory, as well as for transport of tissue specimens from PLANS to Oxford for further analysis. At the end of the enrolment period (31st August 2013 for cases, 4th September 2013 for controls) the PhD candidate was involved in data cleaning and retrieval of missing data on PERCH cases and controls in order to achieve as complete a data set as possible for analysis. He participated in two study wrap-up meetings, hosted by the study co-ordinators at Windsor (United Kingdom) on 2nd through 8th December 2013 and again on 1st through 4th December 2014 at which the results of preliminary analyses of the PERCH data were discussed, and the approach to analysis of the data for the main aetiology paper(s) were finalised. The PhD candidate also attended a two-week long writing workshop at the

Johns Hopkins Bloomberg School of Public Health (Baltimore, Maryland, United States) **478**

from 29th April through 14th May 2015 at which the first of the papers emanating from this thesis [484], was drafted. Under the PhD candidate's leadership, the South African site – which had the smallest complement of study-specific staff members and the most rapid staff turn-over of all the PERCH sites [477] – was able to enrol the largest complement of participants into the study. 2.6Ethical Considerations The studies included in this thesis were

approved by the Human Research Ethics Committee (Medical) **(HREC) of the University of the Witwatersrand,** and **the** **586**

CHBAH Medical Advisory Committee (MAC), Johannesburg (Appendix F), as well as

the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health, Baltimore, **597**

Maryland, United States. All participants were enrolled into the study only

after written informed consent had been obtained from parent(s) **or legal** **480**

guardians. As all participants were <5 years of age, there was no need to obtain assent from the participants themselves. 2.7A Note on the Representation of Numbers in this Thesis Throughout this document,

numbers exceeding three digits (excluding years) are presented with spaces between every third digit on either side of the decimal point, according to the method recommended by both the

National Institute of Standards and Technology and the **Bureau International des Poids et Mesures** [516, 517]. Hence, **the** 618

numbers 1234, 12345, 123456 and 1234567 would be typed as 1 234, 12 345, 123 456 and 1 234 567, respectively. 3 Characteristics of the South African PERCH Cohort & Clinical Presentation of Cases This Chapter presents the characteristics of the South African PERCH cohort, including the numbers of children screened in each of the three groups of interest: cases

with WHO-severe and very severe pneumonia (according to 34

pre-2012 criteria), community controls, and HIV-infected controls (Section 3.1). In Sections 3.2 and 3.3, comparative analyses of the clinical characteristics of

HIV-uninfected cases and their **controls, and HIV-infected cases and** their **controls** 680

are presented. Additionally, the clinical presentations – stratified by HIV-infection status – of pneumonia cases with radiologically-confirmed pneumonia are contrasted against the clinical presentation of cases with normal chest radiographs, as are the

clinical characteristics of cases with and without very severe pneumonia. **The** 955

clinical characteristics of cases dying from pneumonia are then contrasted against those of children surviving to hospital discharge. The basic microbiology of bacterial pneumonia in the cases is presented in Sections 3.2 and 3.3, as is an interrogation of MCPP cases in the South African PERCH cohort (Section 3.4). Finally, a synopsis of pertinent findings from the analyses conducted in this Chapter are presented in point form (Section 3.5). 3.1The PERCH South African Cohort Over the 24-month enrolment period, 920 cases and 964 controls were enrolled into PERCH at the South African site. Screening procedures, and attrition according to protocol-defined exclusion criteria are detailed in this section. 3.1.1Cases The 920 cases represented 44% of all age-eligible

children presenting with WHO-defined severe or very **severe pneumonia** 751

during screening hours at the site that were eligible for enrolment into PERCH (n=2 083) (Figure 3.1). Reasons for non-enrolment of age-eligible

cases with WHO-defined severe or very severe pneumonia 18

included – amongst others – legal guardian refusal to sign consent (15.3%), presenting for admission afterhours (7.6%), absence of a legal guardian to sign consent (5.8%) and the child having been sent for admission to the short-stay ward (5.3%) 87 PERCH study activities at South African site (17/08/2011 to 31/08/2013) PERCH screening days: 598 (80.2%) of the 746 days of the study time period 6 723 (88.6%) age- eligible children screened 2 878 (42.8%) no history of cough and/ or difficulty breathing 13 251 Paediatric admissions 8 927 (67.4%) age- eligible for PERCH 4 106 (46.0%)a with pneumonia and age-eligible for PERCH 9 995 (75.4%) of total Paediatric admissions 7 588 (75.9%) age- eligible for PERCH 3 516 (46.3%)a with pneumonia and age- eligible for PERCH 3 845 (57.2%) with history of cough and/ or difficulty breathing 2 721 (70.8%) age- eligible with severe/ very severe pneumonia 1 124 (29.2%) no signs of severe/ very severe pneumonia 327 (12.0%) not from catchment area 285 (10.5%) recent hospitalisation 26 (1.0%) recently enrolled as a PERCH case 361 (17.3%) reason not stated 319 (15.3%) refused consent 115 (12.5%) HIV-infected 298 (32.4%) HIV-exposed, -uninfected (HEU) 465 (50.5%) HIV-unexposed 2 083 (76.6%) age-eligible children

with severe/ very severe pneumonia, eligible for 980

PERCH enrolment 158 (7.6%) out of screening hours 120 (5.8%) no legal guardian to sign consent 111 (5.3%) inadequate follow-up time 59 (2.8%) met quota 42 (4.6%) HIV exposure status unknown 920 (44.2%) age-eligible with severe/ very severe pneumonia enrolled 18 (0.9%) screening error 17 (0.8%) other 3.

South African PERCH Cohort & Clinical Presentation of Cases 88 Fig. 3.1: CONSORT Diagram of Case Enrolments into PERCH – South African Site a According to the Paediatric Database, 3 908 PERCH age-eligible children had a discharge diagnosis of pneumonia, as did 3 318 of those seen on PERCH screening days: 198 (21.5%) of the 920 PERCH cases were not assigned a primary discharge diagnosis of 'pneumonia' by ward clinicians, but fulfilled

criteria for WHO-defined severe or very severe pneumonia. 26

(Figure 3.1). Of the cases, 115 (12.5%) were HIV-infected, and of the 805 HIV-uninfected cases 298 (37.0%) were HEU, 465 (57.8%) were HIV-unexposed and 42 (5.2%) had undetermined HIV infection exposure status (Figure 3.1). Six-hundred, twenty-two (67.6%) of the cases had severe pneumonia, and of the 883 children with an available chest radiograph 524 (59.3%) had consolidation and/ or other infiltrates on chest radiograph. 3.1.2Community Controls During community control recruitment proceedings, 2 872 households were screened in the study catchment area. Using a subset (n=1 106, 35.4%) of all households screened in order to determine reasons for non-participation of screened households, half of pre-identified potential community controls were not evaluated because they were not present at the household on the day of the screening visit: 24% due to incorrect address details having been recorded in labour ward admission logs, 21% because the child was not at home, and 5% because the child's family had relocated (Figure 3.2). Three-hundred, eighty-seven (38.1%) of the 1 016 households that were reviewed in detail accepted an invitation to participate in PERCH (Figure 3.2). Extrapolating this acceptance rate back to the full complement of households screened for community controls (n=2 872), meant that 1 094 community controls ought to have been enrolled into the study; however, only 830 (75.9%) of these children presented to the RMPRU Clinic at CHBAH for enrolment into the study as community controls. Of the 830 children recruited into PERCH as community controls at the South African site, two (0.2%) were confirmed to be HIV infected and were reallocated to the HIV-infected control cohort, 225 (27.1%) were HEU, 583 (70.4%) were HIV-unexposed and 20 (2.4%) had undetermined HIV exposure status (Figure 3.2). The refusal rate for participation of community controls in PERCH in the South African catchment area was 1.3% (13/ 1 016 reviewed interactions at community-level) and when extrapolating this back to the overall number of household visited suggests that 37 (1.3%) of the 2 872 visited families refused participation in the study. There was further attrition in the numbers of children actually enrolled as community controls at the South African site in view of the fact that only 830 (75.9%) of the 1 094 imputed participating households presented at the RMPRU clinic for enrolment. Hence, the overall refusal rate for participation of community controls in PERCH at the South African site was 10.5% (37 estimated to have refused participation in the study at interview in the community, 264 non-attendees at the RMPRU clinic, i.e. 301 children overall). 2 872 Households visited 1 016 (35.4%) reviewed for enrolment status 412 (40.6%) method of interview not documented 245 (24.1%) wrong address 209 (20.6%) not at home 51 (5.0%) relocated 45 (4.5%) reason for non- enrolment not stated 25 (2.5%) considering participation in PERCH 24 (2.4%) already enrolled in PERCH as a control 14 (1.4%) child died 582 (57.3%) interviewed per normal PERCH process 22 (2.2%) interviewed by neighbourhood recruitment 2 (0.2%) HIV-infected (reallocated to HIV- infected control cohort) 225 (27.1%) HIV-exposed, -uninfected (HEU) 583 (70.4%) HIV-unexposed 3. South African PERCH Cohort & Clinical Presentation of Cases604 (59.4%) with known method of interview 582 (96.4%) normal enrolments; 22 (3.6%) neighbour- hood enrolments 13 (1.3%) refused 3 (0.3%) child too young 20 (2.4%) HIV exposure status unknown 387 (38.1%) accepted invitation to participate in PERCH 1 094 (38.1%) of the 2 872 visited community control households estimated to have accepted invitation to participate in PERCH 830 (75.9%) of the 1 094 households which agreed to participate in PERCH as community controls were enrolled 90Fig. 3.2: CONSORT Diagram of Community Control Recruitment into PERCH – South African Site Note: a subset of households visited during community control screening visits (n=1 016; light orange) were evaluated for reasons not enrolled into PERCH as community controls (light red), and inform the proportion of all households visited (n=2 872) which accepted an invitation to participate in PERCH; method of recruitment (available from a subset of visits) are highlighted in light green. Boxes highlighted in yellow represent the recruited community control cohort. Dotted lines indicate inferred household denominator, after having taken refusal rates into consideration. Of 604 screening episodes in which the method of recruitment of community controls was recorded, the majority (582, 96.4%) were approached using the protocol-defined method (see Section 2.1.4), and only 22 (3.6%) were approached using the neighbourhood recruitment method (Figure 3.2). 3.1.3HIV-infected Controls The majority (n=2 131, 71.4%) of the 2 984 HIV outpatient clinic attendees screened for eligibility into the study were not age eligible for enrolment into PERCH, and 12% of the age-eligible children

did not reside in the study catchment area 330

(Figure 3.3). Of the 728 age-eligible HIV- infected clinic attendees that fulfilled criteria for inclusion into the study, 134 (18.4%) were recruited into PERCH, and together with the two children that were enrolled as community controls but

were found to be HIV-infected, constituted **the** 136 **HIV-infected** 121

controls against which the 115 HIV-infected cases could be evaluated. 3.2Clinical Presentation & Basic Microbiology in HIV-uninfected Children 3.2.1Clinical Presentation: Case-Control Comparison Demographic

and clinical parameters of HIV-uninfected cases, compared to their controls, are tabulated below (Table 3.1), with statistical comparisons between HIV-uninfected cases with radiologically-confirmed pneumonia and HIV-uninfected controls being highlighted. Demographic and clinical characteristics when stratifying by HIV exposure status were similar to the combined group

of HIV-uninfected children (see below). **HIV-** uninfected cases **with** 988

radiologically-confirmed pneumonia were significantly younger (median age 5

.0 months (IQR, 2.0 to 11 **.0 months)** versus 8 **.0 months (IQR,** 4 **.0 to** 16 **.0 months))** 58

and tended to belong to the lowest socio-economic strata than did controls (adjusted odds ratio (aOR) for cases in the lowest socio-economic tier 4.45; 95% CI, 2.63 to 7.51) (Table 3.1). Furthermore, cases had significantly lower body mass

(median weight-for-age Z-score (WAZ) -1.1 **(IQR, -2.** 4 **to** 80

0.1) versus 0.2 (IQR, -0.6 to 1.0)), had higher CRP levels (median 16.9 mg/L (IQR, 4.7 to 51

.0 mg/L) versus 1.0 mg/L 562

(IQR, 0.3 to 3.5 mg/L)) and were more likely to have serum antibiotic activity (54.2% versus 1.0%) than controls (Table 3.1). Overall, HIV-uninfected cases were significantly under-vaccinated with PCV compared to controls (66.7% versus 74.2%:

aOR 0. 57; **95% CI, 0.** 44 **to 0.** 75) **(Table 3.** 767

1). 2 984 HIV Clinic attendees during PERCH screening days 2 131 (71.4%) not age eligible 853 (28.6%) age-eligible HIV-infected children 100 (11.7%) not from catchment area 18 (2.1%) recently enrolled as a PERCH case 4 (0.5%) recent hospitalisation 3 (0.4%) unconfirmed HIV status 728 (85.3%) age-eligible HIV-infected children, eligible for PERCH enrolment 478 (65.7%) reason not stated 63 (8.7%) refused consent 30 (4.1%) screening error 12 (1.6%) no legal guardian to sign consent 2 HIV-infected community controls included in HIV- infected control cohort 134 (18.4%) enrolled as HIV-infected controls 136 South African HIV-infected controls 6 (0.8%) resident in children's home 4 (0.5%) enrolled in another study 1 (0.1%) child did not accompany guardian to the clinic 3. South African PERCH Cohort & Clinical Presentation of Cases 92 Fig. 3.3: CONSORT Diagram of HIV-infected Control Recruitment into PERCH – South African Site It was evident that a seasonal effect came into prominence, with fewer cases presenting in summer in the combined group of HIV-uninfected children (15.4%) compared to the winter months (39.1%) (Table 3.1). HEU and HIV-unexposed children When stratifying by HIV exposure status, HEU cases with radiologically-confirmed pneumonia were younger than their controls (median 5

.0 months (IQR, 2.0 to 10 **.0)** versus 9.0 **months** (IQR, 4 **.0** 58

to 16.0); aOR 0.95

(95% CI, 0. 93 **to 0.** 97), adjusted **P<0.001** 1) **and were more likely to** 628

be impoverished than HEU controls

(aOR 3. 54; **95% CI, 1.** 52 **to** 8.25, adjusted **P=0.** 331

009). HEU cases with radiologically-confirmed disease were also significantly

more likely to have lower weight-for-age 864

(median WAZ -1.4 (IQR, -2.5 to 0.0) versus 0.1 (IQR, -0.7 to 0.9); aOR 0.58

(95% CI, 0. 50 **to 0.** 68), adjusted **P<0.001) and** to have **higher** 727

serum CRP levels (median 14.1 mg/L (IQR, 3.1 to 47

.0 mg/L) versus 1.0 mg/L 562

(IQR, 0.3 to 3.5 mg/L);

aOR 1. 14 (95% CI, 1. 06 to 1. 23), adjusted P<0. 228

001) than HEU controls. HEU cases had a 306-fold (95% CI, 39.97 to 2 340) higher odds of having serum antibiotic activity at enrolment than did HEU controls, adjusted P<0.001. In HIV-unexposed children, cases with

radiologically-confirmed pneumonia were significantly younger than 585

their controls (median 6

.0 months (IQR, 2.0 to 13.0 months) versus 7 .0 months (IQR, 4 .0 to 15 .0 months); aOR 0. 58

97

(95% CI, 0. 96 to 0. 99), adjusted P<0.001) and had 322

a 52% (95% CI, 32% to 66%) lower adjusted odds of being up-to-date with PCV immunisations than HIV-unexposed controls, adjusted P<0.001. As per the observation

in the HIV-uninfected group overall and the HEU group 132

of children, HIV-unexposed cases with radiologically-confirmed pneumonia had significantly lower weight-for-age compared to controls (median WAZ -0.9 (IQR, -2.0 to 0.1) versus 0.2 (IQR, -0.6 to 1.0);

aOR 0.56 (95% CI, 0. 49 to 0. 63), adjusted P<0. 001), and 322

had higher serum CRP levels (median 19.4 mg/L (IQR, 5.6 to 52.5 mg/L) versus 0.9 mg/L (IQR, 0.3 to 3

.1 mg/L); aOR 1. 17 (95% CI, 1. 11 to 1. 305

23), adjusted P<0.001). Serum antibiotic activity at enrolment into PERCH was also significantly higher in HIV-unexposed cases (53.8%) compared to their controls (1.1%) (aOR 99.28; 95% CI, 42.55 to 231.63), adjusted P<0.001. 1 P-values in these analyses were adjusted using the Benjamini-Hochberg procedure. Tab. 3

.1: Demographic and Clinical Characteristics of HIV-uninfected Cases and Controls 814

All Cases Abnormal CXR All Controls aOR (95% CI)a P-valueb Total 805 435/771 (56.4) 828 Age (months) (median, IQR) 5.0 (2.0 to 12.0; n=805) 5.0 (2.0 to 11.0; n=435) 8.0 (4.0 to 16.0; n=828) 0.96 (0.95 to 0.98) <0.001 Age category 1 to 5 months 409/805 (50.8) 219/435 (50.3) 320/828 (38.6) Ref 6 to 11 months 192/805 (23.9) 111/435 (25.5) 228/828 (27.5) 0.70 (0.53 to 0.93) 0.026 12 to 23 months 140/805 (17.4) 78/435 (17.9) 148/828 (17.9) 0.74 (0.53 to 1.02) 0.099 24 to 59 months 64/805 (8.0) 27/435 (6.2) 132/828 (15.9) 0.28 (0.18 to 0.45) <0.001 Sex Male 428/805 (53.2) 213/435 (49.0) 404/828 (48.8) Ref Female 377/805 (46.8) 222/435 (51.0) 424/828 (51.2) 0.99 (0.78 to 1.26) 0.973 Season Spring (Sep to Nov) 178/805 (22.1) 90/435 (20.7) 186/828 (22.5) 0.78 (0.56 to 1.07) 0.172 Summer (Dec to Feb) 143/805 (17.8) 67/435 (15.4) 166/828 (20.0) 0.63 (0.45 to 0.90) 0.021 Autumn (Mar to May) 191/805 (23.7) 108/435 (24.8) 182/828 (22.0) 1.01 (0.74 to 1.38) 0.973 Winter (Jun to Aug) 293/805 (36.4) 170/435 (39.1) 294/828 (35.5) Ref 3. South African PERCH Cohort & Clinical Presentation of Cases 94RTI (Controls only) 44/828 (5.3) Continued on next page . . . Tab. 3.1, continued from previous page . . . DTP-Hib vaccination status All CasesAbnormal CXR All Controls aOR (95% CI)a P-valueb Not up-to-date 265/752 (35.2) 144/408 (35.3) 225/811 (27.7) Ref Up-to-date 487/752 (64.8) 264/408 (64.7) 586/811 (72.3) 0.77 (0.59 to 0.99)0.071 PCV vaccination status Not up-to-date 247/752 (32.8) 136/408 (33.3) 209/811 (25.8) Ref Up-to-date 505/752 (67.2) 272/408 (66.7) 602/811 (74.2) 0.57 (0.44 to 0.75)<0.001 Measles vaccination status Not up-to-date 533/750 (71.1) 293/407

(72.0) 460/812 (56.7) Ref Up-to-date 217/750 (28.9) 114/407 (28.0) 352/812 (43.3) 0.81 (0.56 to 1.17)0.334 Socio-economic status Lowest tier 104/805 (12.9) 63/435 (14.5) 31/823 (3.8) 4.45 (2.63 to 7.51)<0.001 Low-to-mid tier 224/805 (27.8) 130/435 (29.9) 175/823 (21.3) 1.71 (1.18 to 2.49) 0.011 Mid-to-upper tier 340/805 (42.2) 174/435 (40.0) 461/823 (56.0) 0.90 (0.64 to 1.27)0.645 Upper tier 137/805 (17.0) 68/435 (15.6) 156/823 (19.0) Ref Weight-for-age Z-score

(median, IQR) Weight-for-age category (Z- scores) -0.7 (-2. 1 to 0. 759

2; n=800) -1.1 (-2.4 to 0.1; n=430) 0.2 (-0.6 to 1.0; n=821) 0.55 (0.51 to 0.61)<0.001 3. South African PERCH Cohort & Clinical Presentation of Cases 95 >-2 586/800 (73.2) 295/430 (68.6) 784/821 (95.5) Ref ≥-3 to <-2 105/800 (13.1) 64/430 (14.9) 27/821 (3.3) 6.28 (3.90 to 10.12)<0.001 <-3 109/800 (13.6) 71/430 (16.5) 10/821 (1.2) 17.20 (8.71 to 34.00)<0.001 Continued on next page . . . 3. South African PERCH Cohort & Clinical Presentation of Cases 96 Tab. 3.1, continued from previous page . . . All Cases Abnormal CXR All Controls aOR (95% CI)a P-valueb CRP mg/L (median, IQR) 12.0 (2.8 to 39.9; n=783) 16.9 (4.7 to 51.0; n=422) 1.0 (0.3 to 3.5; n=151) 1.17 (1.12 to 1.22) <0.001 CRP ≥40 mg/L No 587/783 (75.0) 290/422 (68.7) 151/151 (100.0) Ref Serum antibiotic activity Yes 196/783 (25.0) 132/422 (31.3) 0/151 (0.0) · · · · · · Yes 375/768 (48.8) 224/413 (54.2) 8/764 (1.0) 111.85 (53.95 to 231.90) <0.001 a Odds ratio adjusted for age in months and season; b P-values adjusted using the Benjamini-Hochberg procedure to guard against false assignment of statistical significance in multiple comparisons; Statistical comparison is between

cases with radiologically -confirmed pneumonia and controls 105

– significant results are highlighted in bold font.

CRP = C-reactive protein; CXR = chest radiograph; 105

Dec to Feb = December through February; DTP

-Hib = diphtheria, tetanus, pertussis, H. influenzae type b vaccine; 129

IQR = interquartile range; Jun to Aug = June through August; Mar to May = March through May; PCV = pneumococcal conjugate vaccine; Ref = Referent; RTI = respiratory tract infection; Sep to Nov = September through November; Table produced using the stargazer package in R [66]. There was insufficient statistical power to discern any significant differences between cases with

radiologically-confirmed pneumonia and controls in the group of HIV-uninfected children 398

with undetermined -exposure status (data not shown). 3.2.2Clinical Presentation: Case-Case Comparison The clinical presentation of HIV-uninfected cases, stratified by radiographic findings (abnormal versus normal chest radiographs), pneumonia severity (very severe versus severe) and outcome (in-hospital death versus survival to hospital discharge) are presented in this subsection. Chest radiographic findings Factors significantly associated with radiologically-confirmed pneumonia amongst HIV-uninfected cases included female sex

(aOR 1. 61; 95% CI, 1. 17 to 2. 21, adjusted P=0. 228

024 1) and severe malnutrition (aOR 2.31;

95% CI, 1.35 to 3. 92, adjusted P=0. 015). HIV-uninfected children 399

with radiologically-confirmed pneumonia also had significantly longer hospital admission than did those with normal chest radiographs

(aOR 1. 05; 95% CI, 1. 03 to 1. 08, adjusted P<0. 228

001),

were more likely to present with fever (aOR 2. 24; 95% CI, 1.62 to 3.11, adjusted P<0. 71

001), to have a serum CRP level ≥40.0 mg/L

(aOR 2. 55; 95% CI, 1. 69 to 3. 85, adjusted P< 852

0.001) and to have serum antibiotic activity at enrolment into PERCH

(aOR 1. 73; 95% CI, 1. 25 to 2. 40, adjusted P=0. 008). The 741

presence of auscultatory wheeze was noted in 29.0% (122/421) of HIV-uninfected children with radiologically-confirmed pneumonia, and 42.6% (104/244) of those with normal chest radiographs

(aOR 0. 56; 95% CI, 0. 40 to 0. 78, adjusted P=0. 358

008). Pneumonia severity HIV-uninfected cases with very severe pneumonia (259/805; 32.2%) were more likely than those with severe pneumonia to have a longer hospital admission (median 7.0 days (IQR, 4.0 to 11.0 days) versus 6.0 days (4.0 to 8.0 days);

aOR 1.02 (95% CI, 1.01 to 1.04), adjusted P=0. 331

045)

and were significantly more likely to be started on supplemental oxygen therapy on 752

admission (aOR 2.87; 1 See footnote on page 93 95% CI, 1.56 to 5.30, adjusted P=0.023 1), to be hypoxaemic

(aOR 1. 74; 95% CI, 1. 21 to 2. 52, adjusted P=0. 228

041) and to have audible wheezing (aOR 2.39;

95% CI, 1. 41 to 4. 04, adjusted P=0. 023). HIV- 856

uninfected

cases with very severe pneumonia were also significantly more likely to have serum antibiotic 362

activity on admission (147/249; 57.0%) than were children with severe pneumonia (233/519; 44.9%) (aOR 1.60; 95% CI, 1.18 to 2.17, adjusted

P=0. 041). In-hospital mortality Twenty (2. 5%) of the 805 HIV-uninfected children 790

died. Lethargy (aOR 14.53; 95% CI, 5.53 to 38.20, adjusted P<0.001) and difficulty feeding (aOR 12.75; 95% CI, 4.37 to 37.15, adjusted P<0.001) at admission to hospital were the two clinical parameters most strikingly associated with in-hospital death amongst HIV-uninfected cases. Being moderately malnourished

was also associated with in-hospital mortality (aOR 4.59; 95% CI, 1. 793

66 to 12.64, adjusted P=0.034) in HIV-uninfected cases. Difficulty feeding was also significantly associated with in-hospital mortality in HEU and HIV- unexposed cases (aOR 17.58 (95% CI, 3.44 to 89.82; adjusted P=0.034) and aOR 12.91 (95% CI, 2.74 to 60.77; adjusted P=0.023), respectively). Furthermore, in HIV-unexposed cases, lethargy was strongly associated with in-hospital mortality (aOR 36.55; 95% CI, 9.55 to 139.85; adjusted P<0.001). 3.2.3Microbiology Results The microbiologic results of HIV-uninfected cases, including those of HEU and HIV-unexposed children, are summarised in Table 3.2. Eight-hundred and two (99.6%) of the 805 HIV-uninfected cases had available blood culture results, and 17 (2.1%) of these cultured clinically significant isolates. Gram negative bacteria accounted for 10 (58.8%) of the 17 clinically-relevant blood culture isolates, however in children with radiologically-confirmed pneumonia, Gram positive

organisms (Enterococcus faecium (n=2) and S. aureus (n=3)) predominated (5/9, 55.6%) (Table 3.2). Viable pneumococcus was not cultured from blood in this cohort, although one HIV-unexposed child with radiologically-confirmed pneumonia had a flag-positive culture-negative blood culture specimen which tested positive for pneumococcus on latex antigen testing. The highest blood 1 See footnote on page 93 Tab. 3.2: Microbiology Results for HIV-uninfected Cases Category All cases (n=805) (%) CXR+ Cases (n=435) (%) Died in Hospital (n=20) (%) HEU (n=298) (%) HIV-unexposed (n=465) (%) Unknown Exposure (n=42) (%) Total blood cultures 802/805 (99.6) 433/435 (99.5) 20/20 (100.0) 296/298 (99.3) 464/465 (99.8) 42/42 (100.0) Contaminants 106/802 (13.2) 67/433 (15.5) 3/20 (15.0) 36/296 (12.2) 59/464 (12.7) 11/42 (26.2) Significant isolates 17/802 (2.1) 9/433 (2.1) 3/20 (15.0) 5/296 (1.7) 12/464 (2.6) 0/42 (0.0) Gram negatives 10/17 (58.8) 4/9 (44.4) 2/3 (66.7) 2/5 (40.0) 8/12 (66.7) · · · E. coli 3 1 0 0 3 0 H. influenzae 2 2 0 1 1 0 K. pneumoniae 1 0 0 0 1 0 M. catarrhalis 1 0 1 0 1 0 N. meningitidis 1 0 0 0 1 0 P. aeruginosa 1 0 1 1 0 0 Salmonella spp. 1 1 0 0 1 0 Gram positives 7/17 (41.2) 5/9 (55.6) 1/3 (33.3) 3/5 (60.0) 4/12 (33.3) · · · E. faecium 2 2 0 2 0 0 S. aureus 5 3 1 1 4 0 Flag positive, blood culture negative Pneumococcal latex positive 1 1 0 0 1 0 Continued on next page . . . 99 Category All cases (n=805) (%) CXR+ Cases (n=435) (%) Died in Hospital (n=20) (%) HEU (n=298) (%) HIV-unexposed (n=465) (%) Unknown Exposure (n=42) (%) Pleural fluid culture No organism detected 4 4 1 2 2 · · · S. aureus 1 1 0 1 0 · · · Pleural fluid PCR No organism detected 2 2 1 1 1 · · · PNEU 2 2 0 1 1 · · · SAUR 1 1 0 1 0 · · · Lung aspirate PJP microscopy 1/5 (20.0) 1/5 (20.0) · · · 0/2 (0.0) 1/3 (33.3) · · · Pos 0/1 (0.0) 0/1 (0.0) · · · · · · 0/1 (0.0) · · · Lung aspirate culture No organism detected 5 5 · · · 2 3 · · · Lung aspirate PCR No organism detected 2 2 · · · 1 1 · · · ADENO, CPNEU 1 1 · · · 1 0 · · · H MPV, HINF, MCAT 1 1 · · · 0 1 · · · HINF, PNEU 1 1 · · · 0 1 · · · Continued on next page . . . 100 Category All cases (n=805) (%) CXR+ Cases (n=435) (%) Died in Hospital (n=20) (%) HEU (n=298) (%) HIV-unexposed (n=465) (%) Unknown Exposure (n=42) (%) Number of children with IS 740/805 (91.9) 387/435 (89.0) 8/20 (40.0) 269/298 (90.3) 433/465 (93.1) 37/42 (88.1) specimens IS PJP microscopy 550/740 (74.3) 304/387 (78.6) 4/8 (50.0) 190/269 (70.6) 329/433 (76.0) 31/37 (83.8) Pos 2/550 (0.4) 0/304 (0.0) 0/4 (0.0) 1/190 (0.5) 1/329 (0.3) 0/31 (0.0) Number of children with ETT 65/805 (8.1) 51/435 (11.7) 10/20 (50.0) 30/298 (10.1) 32/465 (6.9) 3/42 (7.1) specimens ETT PJP microscopy 37/65 (56.9) 31/51 (60.8) 5/10 (50.0) 18/30 (60.0) 18/32 (56.3) 1/3 (33.3) Pos 0/37 (0.0) 0/31 (0.0) 0/5 (0.0) 0/18 (0.0) 0/18 (0.0) 0/1 (0.0) ADENO = adenovirus; CPNEU = C. pneumoniae ; CXR+ = radiologically-confirmed pneumonia; ETT = endotracheal tube; GA = gastric aspirate; HEU = HIV-exposed, -uninfected; HINF = H. influenzae non-type b; HMPV = human metapneumovirus; IS = induced sputum; MCAT = M. catarrhalis ; Mtb = M. tuberculosis ; Neg = negative; PCR = polymerase chain reaction; PJP = P. jirovecii ; PNEU = S. pneumoniae ; Pos = positive; SAUR = S. aureus ; Table produced using the stargazer package in R [66]. 101 3. South African PERCH Cohort & Clinical Presentation of Cases 102 culture positivity rate was observed in those children that died in-hospital, in whom 3 (15.0%) of 20 cultured clinically significant bacteria on blood culture: M. catarrhalis, P. aeruginosa, and S. aureus (Table 3.2). No organism was cultured from PF in four of five children that underwent pleural tap, and S. aureus was cultured in one. Of the four culture-negative PF specimens, pneumococcus was detected by PCR on two. The PF specimen that was culture-positive for S. aureus was also PCR positive for that organism (Table 3.2). All five LA samples were culture-negative for bacterial pathogens but three of the five were positive for multiple organisms on PCR testing: one was positive for adenovirus and C. pneumoniae, another for HMPV, non-type b

H. influenzae and M. catarrhalis, and **the** third **for** 153

non-type b H. influenzae and pneumococcus (Table **3.** 154

2). Seven-hundred, forty (91.9%) of the 805 HIV-uninfected children had IS specimens collected of which 550 (74.3%) were submitted for immunofluorescence testing for P. jirovecii. Immunofluor- escent testing had poor yield, with two (0.4%) of 550 tested specimens being positive: one in an HEU child and another in a child that was HIV-unexposed (Table 3.2). In the 65 HIV-uninfected children that had ETT specimens collected, 37 (56.9%) had specimens subjected to immunofluorescence testing for P. jirovecii and none were positive (Table 3.2). 3.3Clinical Presentation & Basic Microbiology in HIV-infected Children 3.3.1Clinical Presentation: Case-Control Comparison HIV-infected cases with radiologically-confirmed pneumonia were significantly underweight-for- age (aOR 4.14; 95% CI, 2.03 to 8.41) and were 16-fold (95% CI, 1.91 to 137.45) more likely to have a CRP level ≥40 mg/L compared to controls (Table 3.3). Marked disparities in co-trimoxazole prophylaxis (46.4% versus 77.4%), CD4+ T-lymphocyte percentages (14.0% (95% CI, 8.5% to 22.9%) versus 27.4% (95% CI, 21.7% to 34.3%)), and HIVVLs (6.14 log10 RNA copies/mL (IQR, 5.59 to 6.72 RNA copies/mL) versus 4.99 RNA copies/mL (IQR, 2.96 to 6.23 RNA copies/mL)) were appreciated in this comparison, reflecting the inherent bias of our HIV-infected control enrolment strategy which targeted children already in-care and attending outpatient HIV Clinics at the study hospital. Case CD4+ T-lymphocyte counts and percentages were significantly lower 3. South African PERCH Cohort & Clinical Presentation of Cases 103 Tab. 3

.3: Demographic and Clinical Characteristics of HIV-infected 926

Cases and Controls All Cases Abnormal chest radiograph All Controls aOR (95% CI)a P-valueb Total 115 89/112 (79.5) 136 Age (months) (median, IQR) 7.0 (3.0 to 13.5; n=115) 7.0 (3.0 to 14.0; n=89) 9.5 (4.5 to 20.5; n=136) 0.98 (0.96 to 1.00) 0.153 Age category 1 to 5 months 49/115 (42.6) 35/89 (39.3) 45/136 (33.1) Ref 6 to 11 months 34/115 (29.6) 27/89 (30.3) 40/136 (29.4) 0.84 (0.43 to 1.63) 0.845 12 to 23 months

17/115 (14.8) 16/89 (18.0) 21/136 (15.4) 0.98 (0.44 to 2.16) 1.000 24 to 59 months 15/115 (13.0) 11/89 (12.4) 30/136 (22.1) 0.47 (0.20 to 1.07) 0.150 Sex Male 58/115 (50.4) 47/89 (52.8) 58/136 (42.6) Ref Female 57/115 (49.6) 42/89 (47.2) 78/136 (57.4) 0.61 (0.35 to 1.06) 0.153 Season Spring (Sep to Nov) 40/115 (34.8) 30/89 (33.7) 43/136 (31.6) 0.98 (0.46 to 2.09) 1.000 Summer (Dec to Feb) 19/115 (16.5) 14/89 (15.7) 16/136 (11.8) 1.19 (0.47 to 3.02) 0.939 Autumn (Mar to May) 32/115 (27.8) 26/89 (29.2) 49/136 (36.0) 0.75 (0.35 to 1.61) 0.664 Winter (Jun to Aug) 24/115 (20.9) 19/89 (21.3) 28/136 (20.6) Ref RTI (Controls only) 6/136 (4.4) Continued on next page . . . Tab. 3.3, continued from previous page . . . DTP-Hib vaccination status All CasesAbnormal chest radiograph All Controls aOR (95% CI)a P-valueb Not up-to-date 36/107 (33.6) 29/81 (35.8) 29/91 (31.9) Ref Up-to-date 71/107 (66.4) 52/81 (64.2) 62/91 (68.1) 0.86 (0.45 to 1.63)0.855 PCV vaccination status Not up-to-date 34/106 (32.1) 27/81 (33.3) 34/91 (37.4) Ref Up-to-date 72/106 (67.9) 54/81 (66.7) 57/91 (62.6) 1.04 (0.51 to 2.12)1.000 Measles vaccination status Not up-to-date 74/107 (69.2) 53/81 (65.4) 54/90 (60.0) Ref Up-to-date 33/107 (30.8) 28/81 (34.6) 36/90 (40.0) 0.92 (0.40 to 2.08)0.987 Socio-economic status Lowest tier 18/115 (15.7) 15/89 (16.9) 20/135 (14.8) 0.86 (0.32 to 2.31) 0.953 Low-to-mid tier 39/115 (33.9) 31/89 (34.8) 34/135 (25.2) 1.14 (0.47 to 2.77)0.956 Mid-to-upper tier 43/115 (37.4) 29/89 (32.6) 65/135 (48.1) 0.50 (0.21 to 1.18)0.200 Upper tier 15/115 (13.0) 14/89 (15.7) 16/135 (11.9) Ref 3. South African PERCH Cohort & Clinical Presentation of Cases 104

Weight-for-age Z-score (median, **IQR) -2.** 1 **(-3.** 4 **to -1.** **80**

0; n=114) -2.3 (-3.5 to -1.1; n=88) -1.1 (-2.2 to -0.0; n=135) 0.66 (0.54 to 0.79)<0.001 Continued on next page . . . Tab. 3.3, continued from previous page . . . All Cases Abnormal chest radiograph All Controls aOR (95% CI)a P-valueb Weight-for-age category (Z-scores) >-2 55/114 (48.2) 40/88 (45.5) 96/135 (71.1) Ref ≥-3 to <-2 22/114 (19.3) 18/88 (20.5) 22/135 (16.3) 1.92 (0.92 to 4.00) 0.153 <-3 37/114 (32.5) 30/88 (34.1) 17/135 (12.6) 4.14 (2.03 to 8.41) <0.001 CRP mg/L (median, IQR) 21.4 (5.0 to 105.8; n=112) 26.4 (5.8 to 132.5; n=86) 1.3 (0.4 to 2.2; n=27) 1.05 (1.00 to 1.10) 0.068 CRP ≥40 mg/L No 73/112 (65.2) 54/86 (62.8) 26/27 (96.3) Ref Yes 39/112 (34.8) 32/86 (37.2) 1/27 (3.7) 16.20 (1.91 to 137.45) 0.030 Serum antibiotic activity Received prophylactic co-trimoxazole Attended ART clinic in past 3 months Yes 64/110 (58.2) 46/84 (54.8) 16/118 (13.6) 7.26 (3.64 to 14.51)<0.001 Yes 42/86 (48.8) 32/69 (46.4) 103/133 (77.4) 0.24 (0.12 to 0.45)<0.001 Yes 28/49 (57.1) 21/36 (58.3) 117/134 (87.3) 0.19 (0.08 to 0.44)<0.001 3. South African PERCH Cohort & Clinical Presentation of Cases 105 On ART at PERCH enrolment Yes 33/110 (30.0) 24/85 (28.2) 113/136 (83.1) 0.08 (0.04 to 0.16)<0.001 Continued on next page . . . 3. South African PERCH Cohort & Clinical Presentation of Cases 106 Tab. 3.3, continued from previous page . . . All Cases Abnormal chest radiograph All Controls aOR (95% CI)a P-valueb Time on ART (weeks) 0.0 (0.0 to 10.0; n=90) 0.0 (0.0 to 5.4; n=69) 14.6 (4.7 to 40.6; n=133) 0.98 (0.96 to 0.99) <0.001 (median, IQR) CD4 count (median, IQR) 808 (440 to 1372; n=111) 773 (442 to 1319; n=86) 1725 (1176 to 2328; n=133) 0.9987 (0.9983 to 0.9992) <0.001 CD4 % (median, IQR) 14.9 (8.7 to 23.8; n=111) 14.0 (8.5 to 22.9; n=86) 27.4 (21.7 to 34.3; n=133) 0.90 (0.87 to 0.93) <0.001 Immunological stage None 6/111 (5.4) 2/86 (2.3) 47/133 (35.3) Ref Mild 13/111 (11.7) 11/86 (12.8) 17/133 (12.8) 15.44 (3.01 to 79.25) 0.004 Advanced 13/111 (11.7) 11/86 (12.8) 23/133 (17.3) 11.57 (2.30 to 58.18) 0.011 Severe 79/111 (71.2) 62/86 (72.1) 46/133 (34.6) 32.60 (7.25 to 146.64) <0.001 Viral load (median, IQR) 6.18 (5.57 to 6.62; n=97) 6.14 (5.59 to 6.72; n=75) 4.99 (2.96 to 6.23; n=96) 1.83 (1.42 to 2.37) <0.001 Viral load categories <100 copies/mL 1/97 (1.0) 0/75 (0.0) 16/96 (16.7) Ref 100-999 copies/mL 0/97 (0.0) 0/75 (0.0) 9/96 (9.4) · · · · · · 1 000-9 999 copies/mL 9/97 (9.3) 7/75 (9.3) 12/96 (12.5) · · · · · · ≥10 000 copies/mL 87/97 (89.7) 68/75 (90.7) 59/96 (61.5) · · · · · · Continued on next page . . . 3. South African PERCH Cohort & Clinical Presentation of Cases 107 Tab. 3.3, continued from previous page . . . All Cases Abnormal chest All Controls aOR (95% CI)a P-valueb radiograph Clinical Stage 1 3/115 (2.6) 1/89 (1.1) 60/136 (44.1) Ref 2 3/115 (2.6) 2/89 (2.2) 3/136 (2.2) 37.17 (2.51 to 551.19) 0.027 3 28/115 (24.3) 21/89 (23.6) 22/136 (16.2) 71.97 (9.00 to 575.48) <0.001 4 81/115 (70.4) 65/89 (73.0) 51/136 (37.5) 93.09 (12.35 to 701.58) <0.001 a Odds ratio adjusted for age in months and season; b P-values adjusted using the Benjamini-Hochberg procedure to guard against false assignment of statistical significance in multiple comparisons; Statistical comparison is between

cases with radiologically **-confirmed pneumonia and controls** **105**

– significant results are highlighted in bold font.

CRP = C-reactive protein; chest radiograph **105**

= chest radiograph; Dec to Feb = December through February; DTP

-Hib = diphtheria, tetanus, pertussis, H. **influenzae type b vaccine;** **129**

IQR = interquartile range; Jun to Aug = June through August; Mar to May = March through May; PCV = pneumococcal conjugate vaccine; Ref = Referent; RTI = respiratory tract infection; Sep to Nov = September through November; Table produced using the stargazer package in R [66]. 3. South African PERCH Cohort & Clinical Presentation of Cases 108 and their degree of immunosuppression was therefore more advanced than controls; furthermore, WHO clinical stage of HIV disease was more advanced in cases than controls (aOR of a case being WHO Stage IV disease 93.09 (95% CI, 12.35 to 701.58) compared to controls) (Table

3.3). 3.3.2Clinical Presentation: Case-Case Comparison Thirty-nine (33.9%) of the 115 HIV-infected cases had WHO-defined very severe pneumonia, and 17 (14.8%) died during the course of their hospitalisation.

The only clinical parameter that was significantly associated **with** **9**

any of the clinical end-points explored above in HIV-uninfected cases – radiologically-confirmed disease, pneumonia severity, in-hospital death – was significantly shorter hospital stay amongst HIV-infected cases that died in-hospital compared to those who survived to hospital discharge, indicating that most deaths amongst HIV-infected pneumonia cases occurred in the first days of hospitalisation

(aOR 0. 04; **95% CI, 0.** 01 **to 0.** 23, adjusted **P<0.** **358**

001 1). Auscultatory wheeze was noted in 14.8% (13/88) HIV-infected children with radiologically- confirmed pneumonia, and 25.0% (3/12) of those with normal chest radiographic findings

(aOR 0. 45; **95% CI, 0.** 10 **to 1.** 99, adjusted **P=0.** **358**

903). 3.3.3Microbiology Results All 115 HIV-infected cases had blood cultures submitted on the day of hospitalisation, and of these nine (7.8%) cultured clinically relevant bacteria. Gram negative organisms predominated overall (isolated in two thirds of the blood culture that were positive with significant organisms): P. aeruginosa

(n=3), E. cloacae (n=1), E. coli **(n=1)** and Salmonella spp. **(n=1)** **71**

(Table 3.4). In HIV-infected children with radiologically-confirmed pneumonia, Gram negative and

Gram positive organisms were isolated **in** three each **of the** six blood **cultures** **386**

that were positive with clinically relevant organisms. As was the case in HIV-uninfected children, the highest blood culture positivity rate was amongst HIV-infected children that died, in whom 3 (17.6%) of 17 cultured Gram negative organisms: P. aeruginosa in two and E. cloacae in one (Table 3.4). Pneumococcus (serotype 16F) was cultured from blood in one

HIV-infected child **with radiologically-confirmed pneumonia, and** another **HIV-infected** child **had** **513**

non-viable pneumococcus detected through latex antigen testing of a flag-positive, culture-negative blood culture specimen (Table 3.4). 1 See footnote on page 93 3. South African PERCH Cohort & Clinical Presentation of Cases 109 Tab. 3.4: Microbiology Results for HIV-infected Cases Category All cases (n=115) (%) CXR+ Cases (n=89) (%) Died in Hospital (n=17) (%) Total blood cultures 115/115 (100.0) 89/89 (100.0) 17/17 (100.0) Contaminants 15/115 (13.0) 13/89 (14.6) 5/17 (29.4) Significant isolates 9/115 (7.8) 6/89 (6.7) 3/17 (17.6) Gram negatives 6/9 (66.7) 3/6 (50.0) 3/3 (100.0) E. cloacae

1 1 1 E. coli 1 1 0 P. aeruginosa 3 **1** **697**

2 Salmonella spp. 1 0 0 Gram positives 3/9 (33.3) 3/6 (50.0) 0/3 (0.0) E. faecium 1 1 0 S. pneumoniae 1 1 0 S. aureus 1 1 0 Flag positive, blood culture negative Pneumococcal latex positive 110 Continued on next page . . . Tab. 3.4, continued from previous page . . . Category All cases CXR+ Cases Died in Hospital (n=115) (%) (n=89) (%) (n=17) (%) Lung aspirate PJP microscopy 1/1 (100.0) 1/1 (100.0) · · · Pos 0/1 (0.0) 0/1 (0.0) · · · Lung aspirate culture No organism detected 11· · · Lung aspirate PCR PNEU 1 1 · · · Number of children with IS specimens IS PJP microscopy 100/115 (87.0) 68/100 (68.0) 80/89 (89.9) 57/80 (71.2) 11/17 (64.7) 9/11 (81.8) Pos 1/68 (1.5) 1/57 (1.8) 0/9 (0.0) Number of children with ETT specimens 7/115 (6.1) 6/89 (6.7) 1/17 (5.9) 3. South African PERCH Cohort & Clinical Presentation of Cases 110 ETT PJP microscopy 3/7 (42.9) 3/6 (50.0)0/1 (0.0) Pos 1/3 (33.3) 1/3 (33.3)· · · CXR+ = radiologically-confirmed pneumonia;

ETT = endotracheal tube; GA = gastric aspirate; **25**

IS = induced sputum; Mtb = M. **tuberculosis ; Neg = negative;** **25**

PCR = polymerase chain reaction; PJP = P. jirovecii ; PNEU = S. pneumoniae ; Pos = positive; Table produced using the stargazer package in R [66]. No HIV-infected child underwent pleural tap for microbiological examination of PF, and only one underwent lung aspiration. The LA specimen was culture negative, but PCR positive for pneumococcus (Table 3.4). One hundred (87.0%) of the 115 HIV-infected cases had IS specimens collected, and of these, 68 were submitted for immunofluorescence testing for P. jirovecii. The yield from immunofluorescence testing for P. jirovecii was poor, with one (1.5%) of 68 IS specimens being positive (Table 3.4). The positivity yield for P. jirovecii immunofluorescence testing was highest in HIV-infected children in whom ETT specimens had been collected on mechanically ventilated children (n=7), in whom one of three was positive for P. jirovecii (Table 3.4). 3.4Microbiologically-confirmed Pneumococcal Cases As can be appreciated from Tables 3.2 and 3.4, there were seven cases with microbiologically- confirmed pneumococcal pneumonia in the South African PERCH cohort: four were HIV-uninfected (one of whom was HEU), and three were HIV-infected. One was blood culture positive for serotype 16F pneumococcus, two were pneumococcal latex antigen positive on flag-positive, culture-negative blood cultures, two were positive for pneumococcus on PF PCR, and two were pneumococcal PCR positive on lung aspirate material. Of note, in these seven cases with microbiologically-confirmed pneumococcal pneumonia all had radiologically-confirmed disease, all were positive for pneumococcus on FTDResp-33 PCR testing of NP/OP and IS specimens, and none died during the course of their hospitalisation (data not shown). The median CRP level in the cases with microbiologically-confirmed pneumococcal pneumonia was 213.9 mg/L (IQR, 162.3 to 262.5 mg/L). 3.5Synopsis of Chapter 3 This Chapter has presented the South African PERCH cohort as a prelude to the ensuing analyses, and may be summarised in the following points: I. 920 cases were enrolled into PERCH at the South African site; (a) 805 HIV-uninfected children, of which 298 (37.0%) were HEU, 465 (57.8%) were HIV- unexposed and 42 (5.2%) had undetermined HIV exposure status; i. 56.4% of HIV-uninfected children with available chest radiographs (n=771) had radiologically-confirmed pneumonia; ii. 32.2% of

HIV-uninfected children presented **with WHO-defined** very **severe pneumonia;** iii. **The** **195**

CFR amongst HIV-uninfected cases was 2.5%; (b) 115

HIV-infected children, most of which (70.0%) **were not on** **60**

ART at enrolment into the study; i. 79.5% of HIV-infected children with available chest radiographs (n=112) had radiologically- confirmed pneumonia; ii. 33.9% of HIV-infected children presented with WHO-defined very severe pneumonia; iii. The CFR amongst HIV-uninfected cases was 14.8%; II. 964 controls were enrolled in addition to the cases, which included: (a) 828 HIV-uninfected children, of which 225 (27.2%) were HEU, 583 (70.4%) were HIV- unexposed and 20 (2.4%) had undetermined HIV exposure status; (b) 136 HIV-infected controls; III. In the comparison between HIV-uninfected cases and their age-frequency matched controls, radiologically-confirmed pneumonia was associated with: (a) Young age, lack of PCV immunisation, low socio-economic status, malnutrition, and season; (b) Children with radiologically-confirmed pneumonia had significantly elevated serum CRP levels and were more likely to have serum antibiotic activity at enrolment than did HIV-uninfected controls; IV. Amongst HIV-infected children, evidence pointed strongly towards an innate bias in our choice of sampling of controls (a captive audience attending two Paediatric ART Clinics at CHBAH), in that: (a) Cases were more likely not to have attended ART clinics or to have been on co-trimoxazole prophylaxis compared to controls; (b) HIV-infected cases had more advanced immunosuppression and clinical disease than did controls; (c) They also had higher HIVVLs and were significantly less likely to have initiated ART prior to enrolment into PERCH; (d) Malnutrition, elevated serum CRP

and the presence of serum antibiotic activity **were significantly associated with** **863**

case status in HIV-infected children; V. In terms of investigation for the microbiologic cause of pneumonia: (a) Blood culture yield for bacterial organisms was low in HIV-uninfected and -infected children (2.1% and 6.7% amongst cases with radiologically-confirmed pneumonia, respectively); (b) Few PF and LA specimens were available for analysis; (c) The highest yield of !FA for PJP was on ETT in HIV-infected children (1 in 3 tested specimens positive); (d) The yield of !FA for PJP on IS specimens was low; (e) Seven MCPP cases were identified in the South African PERCH cohort. 4 Formal Case-Control Analysis of NP/OP & lytA in Whole Blood in the South African PERCH Cohort Chapter 4 presents the marginal and conditional logistic regression outputs from the case-control analysis of organism prevalence in case and control NP/OP swabs and whole blood (for lytA) in the South African PERCH cohort. The subset of cases with radiologically-confirmed pneumonia was designated as being the comparator group in these analyses. As a starting point from which these analyses are derived, raw and organism-density cut-off adjusted prevalence of pathogens in NP/OP and whole blood are presented (Section 4.1). Thereafter, tables containing the logistic regression outputs (Tables 4.1 through 4.4) as well as ‘aetiology pies’ (Figures 4.5 through 4.8) for sub-groups of interest (HEU, HIV-unexposed and HIV-infected children) are presented (Section 4.2). Pneumonia ‘aetiology pies’ are derived using the point estimate of the FA for each pathogen significantly associated with case status: these ‘aetiology pies’ are derived for all cases, cases with radiologically-confirmed pneumonia, and

cases that died in-hospital compared to controls. 4.1NP/OP and lytA Organism prevalence in Cases and Controls 4.1.1Unadjusted Data In the cohort overall, comparing NP/OP and lytA prevalence between cases with radiologically- confirmed pneumonia and controls, there was high NP/OP carriage of pneumococcus (66.7% (348/522) in cases and 67.7% (649/959) in controls), M. catarrhalis (62.5% (326/522) in cases and 64.0% (614/959) in controls), non-type b H. influenzae (57.1% (298/522) in cases and 44.8% (430/959) in controls) and CMV (45.9% (238/518) in cases and 47.1% (452/959) in controls), Figure 4.1. Organisms detected on NP/OP swabs at least twice as frequently in cases compared to controls included B. pertussis (2.1% (11/522) in cases versus 0.4% (4/959) in controls), influenza A (3.5% (18/518) in cases, versus 1.4% (13/959) in controls), influenza B (1.4% (7/518) in cases versus 0.3% (3/959) in controls), HMPV (6.8% (35/517) in cases versus 3.1% (30/959) in controls), parainfluenza virus 1 (2.3% (12/517) in cases versus 0.5% (5/959) in controls), parainfluenza virus 3 (7.1% (37/518) in cases versus 2.2% (21/959) in controls) and RSV (29.3% (152/518) in cases versus 3.1% (30/959) in controls) (Figure 4.1). 114 4. Case-Control Analysis115 Fig. 4.1: Prevalence of Pathogen Detection in NP/OP and Whole Blood Specimens Amongst Children with Radiologically-confirmed Pneumonia in the South African PERCH Cohort: Raw Data Organisms detected in NP/OP swabs, unless otherwise specified. ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus;

HIB = H. influenzae type b; HINF = **H. influenzae** non **-type** 36

b; HMPV = hu- man metapneumovirus; MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type 2;** PARA3 = **parainfluenza virus type 3;** PARA4 = **parainfluenza virus type 4;** 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV =

parechovirus/ enterovirus; RHINO = human **rhinovirus; RSV = respiratory syncytial virus;** 130

SAUR = S. aureus ; WB = whole blood. 4. Case-Control Analysis 116 (a) (b) (c) Fig. 4.2: Prevalence

of Pathogen Detection in **NP/OP and** Whole Blood **Specimens** 329

Amongst Children with Radiologically-confirmed Pneumonia in (a) HEU, (b) HIV-unexposed and (c) HIV-infected Children: Raw Data Organisms detected in NP/OP swabs, unless otherwise specified. ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus; HEU = HIV-exposed, -uninfected;

HIB = H. influenzae type b; HINF = non **-type** b **H. influenzae** 36

; HIV =

human immunodeficiency virus type 1; HMPV = human metapneumovirus; 121

MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type 2;** PARA3 = **parainfluenza virus type 3;** PARA4 = **parainfluenza virus type 4;** 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV =

parechovirus/ enterovirus; RHINO = human **rhinovirus; RSV = respiratory syncytial virus;** 130

SAUR = S. aureus ; WB = whole blood. When stratifying the cohort by HIV infection and -exposure status, marked shifts in pathogen prevalence were observed (Figure 4.2). The highest prevalence of detection of any organism amongst the three groups (HEU, HIV-unexposed and HIV-infected children), was a 79.8% (71/89) NP/OP detection rate of CMV in HIV-infected cases with radiologically-confirmed pneumonia (Figure 4.2). Two-fold greater organism prevalence for each of the three groups (HEU, HIV-unexposed and HIV-exposed children) included: • HEU children: B. pertussis (1.8% (3/164) in cases versus 0.4% (1/224) in controls), coronavirus NL63 (3.7% (6/161) in cases versus 1.3% (3/224) in controls), coronavirus HKU1 (3.7% (6/161) in cases versus 1.3% (3/224) in controls), C. pneumoniae (3.0% (5/164) in cases versus 1.3% (3/224) in controls), influenza A (5.0% (8/161) in cases versus 1.3% (3/224) in controls), HMPV (8.7% (14/161) in cases versus 3.1% (7/224) in controls), parainfluenza virus 4 (3.1% (5/161) in cases versus 0.9% (2/224) in controls) and RSV (31.7% (51/161) in cases versus 2.7% (6/224) in controls); • HIV-unexposed children: B. pertussis (2.4% (6/245) in cases versus 0.5% (3/579) in controls), coronavirus 229E (0.4% (1/224) in cases versus 0.2% (1/579) in controls), influenza B (2.0% (5/244) in cases versus 0.3% (2/579) in controls), HMPV (6.6% (16/243) in cases versus 3.3% (19/579) in controls), parainfluenza virus 1 (3.3% (8/243) in cases versus 0.3% (2/579) in controls), parainfluenza virus 3 (7.8% (19/243) in cases versus 1.9% (11/579) in controls) and RSV (34.4% (84/244) in cases versus 3.6% (21/579) in controls); • HIV-infected children: coronavirus NL63 (2.2% (2/89) in cases versus 0.7% (1/136) in controls), HMPV (4.5% (4/89) in cases versus 2.2% (3/136) in controls), parainfluenza virus 3 (12.4% (11/89) in cases versus 2.9% (4/136) in controls), P. jirovecii (31.5% (28/89) in cases versus 5.9% (8/136) in controls), RSV (12.4% (11/89) in cases versus 2.2% (3/136) in controls) and S. aureus (47.2% (42/89) in cases versus 20.6% (28/136) in controls). Pneumococcal DNAemia prevalence was lower in HEU and HIV-unexposed cases with radiologically-confirmed pneumonia compared to controls, however the opposite was true in HIV-infected children in whom case pneumococcal prevalence was higher in whole blood than controls (14.6% (13/89) in cases versus 8.8% (12/136) in controls) (Figure 4.2). 4.1.2Adjusted Data Cut-off densities which best distinguished case from control status – using cases with abnormal chest radiograph findings as the target group of interest – are tabulated in Appendix G (Table G.1). When applying the threshold density cut-offs to the study cohort by using the scheme adopted in Section 2.4.2, certain pathogens that were not as prominently associated with case status in the unrefined analysis (Section 4.1.1) were more strikingly associated with case status. These included, amongst the viruses, adenovirus (7.3% (38/518) in cases versus 3.0% (29/959) in controls) and human rhinovirus (8.1% (42/518) in cases versus 4.3% (41/959) in controls) and, amongst bacterial pathogens, non-type b H. influenzae (21.8% (114/522) in cases versus 7.5% (72/959) in controls), M. catarrhalis (11.9% (62/522) in cases versus 5.8% (56/959) in controls), S. pneumoniae in NP/OP swabs (16.5% (86/522) in cases versus 8.8% (84/959) in controls) and whole blood (7.5% (39/521) in cases versus 4.8% (46/963) in controls), and S. aureus (13.4% (70/522) in cases versus 5.8% (56/959) in controls) (Figure 4.3). Pneumocystis jirovecii also came into prominence amongst cases once a cut-off density threshold had been applied (8.4% (44/522) in cases versus 1.3% (12/959) in controls) (Figure 4.3). As was the situation in the stratified analysis of unadjusted pathogen prevalence, marked shifts in pathogen prevalence were observed in the three groups of interest (HEU, HIV-unexposed and HIV-infected children) after applying organism density cut-offs to the data (Figure 4.4). The highest prevalence of detection of any organism amongst the three groups (HEU, HIV-unexposed and HIV-infected children), was a 46.1% (41/89) NP/OP detection rate of CMV in HIV-infected cases with radiologically-confirmed pneumonia (Figure 4.2). After applying organism density cut-offs according to the scheme described in Section 2.4.2, the following additional organisms came into prominence as being twice as prevalent in cases compared to controls (Figure 4.4): • HEU children: adenovirus (9.3% (15/161) in cases versus 4.5% (10/224) in controls), H. influenzae type b (1.2% (2/164) in cases versus 0.4% (1/224) in controls), non-type b H. influenzae (14.0% (23/164) in cases versus 0.9% (2/224) in controls), P. jirovecii (6.7% (11/164) in cases versus 0.9% (2/224) in controls) and pneumococcus on NP/OP (6.1% (10/164) in cases versus 2.2% (5/224) in controls); 4. Case-Control Analysis119 Fig. 4.3: Prevalence of Pathogen Detection in NP/OP and Whole Blood Specimens Amongst Children with Radiologically-confirmed Pneumonia in the South African PERCH Cohort: Adjusted Data Organisms detected in NP/OP swabs, unless otherwise specified. ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = coronavirus OC43; COR63 = coronavirus NL63; CORHKU = coronavirus HKU1; 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = human 45

bocavirus;

HIB = H. influenzae type b; HINF = non -type b H. influenzae 36

; HMPV = hu- man metapneumovirus; MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = parainfluenza virus type 2; PARA3 = parainfluenza virus type 3; PARA4 = parainfluenza virus type 4; 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV =

parechovirus/ enterovirus; RHINO = human rhinovirus; RSV = respiratory syncytial virus; 130

SAUR = S. aureus ; WB = whole blood. 4. Case-Control Analysis 120 (a) (b) (c) Fig. 4.4: Prevalence

of Pathogen Detection in NP/OP and Whole Blood Specimens 329

Amongst Children with Radiologically-confirmed Pneumonia in (a) HEU, (b) HIV-unexposed and (c) HIV-infected Children: Adjusted Data Organisms detected in NP/OP swabs, unless otherwise specified. ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = coronavirus OC43; COR63 = coronavirus NL63; CORHKU = coronavirus HKU1; 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = human 45

bocavirus; HEU = HIV-exposed, -uninfected;

HIB = H. influenzae type b; HINF = non -type b H. influenzae 36

; HIV =

human immunodeficiency virus type 1; HMPV = human metapneumovirus; 121

MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = parainfluenza virus type 2; PARA3 = parainfluenza virus type 3; PARA4 = parainfluenza virus type 4; 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV =

130

parechovirus/ enterovirus; RHINO = human **rhinovirus; RSV = respiratory syncytial virus;**

SAUR = S. aureus ; WB = whole blood. 4. Case-Control Analysis121 • HIV-unexposed children: adenovirus (5.7% (14/244) in cases versus 2.6% (15/579) in con- trols), human bocavirus (2.5% (6/243) in cases versus 0.7% (4/579) in controls), non-type b H. influenzae (24.1% (59/245) in cases versus 9.5% (55/579) in controls) and P. jirovecii (4.1% (10/245) in cases versus 1.4% (8/579) in controls); • HIV-infected children: adenovirus (7.9% (7/89) in cases versus 2.9% (4/136) in controls), CMV (46.1% (41/89) in cases versus 18.4% (25/136) in controls), human bocavirus (12.4% (11/89) in cases versus 5.1% (7/136) in controls), non-type b H. influenzae (30.3% (27/89) in cases versus 9.6% (13/136) in controls), M. catarrhalis (23.6% (21/89) in cases versus 6.6% (9/136) in controls), P. jirovecii (23.6% (21/89) in cases versus 1.5% (2/136) in controls) and pneumococcus on whole blood (10.1% (9/89) in cases versus 2.9% (4/136) in controls). In the analysis of adjusted organism densities, S. aureus retained its prominence amongst cases compared to controls in the HIV-infected group with 19.1% (17/89) of cases with radiologically- confirmed pneumonia carrying the organism in their nasopharynx compared to 5.1% (7/136) of controls. Furthermore, S. aureus exhibited greater prominence in HEU and HIV-unexposed cases after applying the density cut-off adjustment (Figure 4.4). 4.2Logistic Regression Output of NP/OP Swab Organism & lytA Detection – Case Control Analysis Tables 4.1 through 4.4 summarise the results of marginal and conditional logistic regression models, adjusting for age (in months) and season, comparing the organism profiles on NP/OP swabs and in whole blood (for pneumococcus) between cases with radiologically-confirmed pneumonia and controls in the South African PERCH cohort. In addition to adjusting for age (in months) and season, all other pathogens

were adjusted for in the conditional **logistic regression model.** **938**

The 'aetiology pies' depicted in Figure 4.5 also include point estimates of the FA that were derived in the case-control analyses using all cases and cases that died in-hospital so as to describe the pathogen profiles associated with each of those groups, for the entire South African PERCH cohort, HEU children, HIV-unexposed children and HIV-infected children. Tab. 4.1: Marginal and Conditional Odds Ratios of Organism Prevalence in NP/OP Swabs and Whole Blood (Radiologically-confirmed Pneumonia) – All Children Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** **3**

ADENO 38/518 (7.3) 29/959 (3.0) 2.55 (1.55 to 4.20) <0.001 0.04 (0.03 to 0.06) 4.07 (2.31 to 7.17) <0.001 0.06 (0.04 to 0.06) BOPE 11/522 (2.1) 4/959 (0.4) 4.22 (1.32 to 13.44) 0.015 0.02 (0.01 to 0.02) 7.06 (2.01 to 24.74) 0.002 0.02 (0.01 to 0.02) CMV 148/518 (28.6) 224/959 (23.4) 1.13 (0.88 to 1.45) 0.338 · · · 1.15 (0.85 to 1.57) 0.366 · · · COR229 1/518 (0.2) 2/959 (0.2) 0.93 (0.08 to 10.72) 0.951 · · · 2.49 (0.18 to 33.61) 0.493 · · · COR43 15/518 (2.9) 55/959 (5.7) 0.44 (0.24 to 0.79) 0.006 · · · 0.58 (0.28 to 1.21) 0.144 · · · COR63 13/518 (2.5) 27/959 (2.8) 0.93 (0.47 to 1.85) 0.844 · · · 1.77 (0.83 to 3.80) 0.141 · · · CORHKU 9/518 (1.7) 23/959 (2.4) 0.77 (0.35 to 1.70) 0.513 · · · 0.51 (0.19 to 1.34) 0.171 · · · CPNEU 9/522 (1.7) 20/959 (2.1) 1.02 (0.45 to 2.32) 0.964 · · · 0.68 (0.24 to 1.95) 0.474 · · · FLUA 18/518 (3.5) 13/959 (1.4) 3.11 (1.46 to 6.62) 0.003 0.02 (0.01 to 0.03) 4.89 (2.14 to 11.17) <0.001 0.03 (0.02 to 0.03) FLUB 7/518 (1.4) 3/959 (0.3) 5.66 (1.39 to 23.05) 0.016 0.01 (0.00 to 0.01) 4.97 (1.07 to 23.12) 0.041 0.01 (0.00 to 0.01) FLUC 6/522 (1.1) 7/959 (0.7) 1.70 (0.55 to 5.20) 0.354 · · · 1.57 (0.36 to 6.79) 0.547 · · · HBOV 27/517 (5.2) 21/959 (2.2) 2.72 (1.50 to 4.93) 0.001 0.03 (0.02 to 0.04) 2.94 (1.43 to 6.07) 0.003 0.03 (0.02 to 0.04) HIB 6/522 (1.1) 1/959 (0.1) 12.42 (1.46 to 105.31) 0.021 0.01 (0.00 to 0.01) 16.64 (1.81 to 152.88) 0.013 0.01 (0.01 to 0.01) HINF 114/522 (21.8) 72/959 (7.5) 3.51 (2.54 to 4.86) <0.001 0.16 (0.13 to 0.17) 2.82 (1.90 to 4.18) <0.001 0.14 (0.10 to 0.17) HMPV 35/517 (6.8) 30/959 (3.1) 2.29 (1.37 to 3.82) 0.002 0.04 (0.02 to 0.05) 2.76 (1.53 to 4.99) 0.001 0.04 (0.02 to 0.05) MCAT 62/522 (11.9) 56/959 (5.8) 2.04 (1.39 to 3.00) <0.001 0.06 (0.03 to 0.08) 1.51 (0.94 to 2.45) 0.090 · · · Continued on next page . . . 122 Tab. 4.1, continued from previous page . . . Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** **3**

MPNEU 2/517 (0.4) 6/959 (0.6) 0.80 (0.15 to 4.18) 0.795 · · · 1.37 (0.17 to 11.31) 0.771 · · · PARA1 12/517 (2.3) 5/959 (0.5) 5.48 (1.87 to 16.10) 0.002 0.02 (0.01 to 0.02) 8.57 (2.71 to 27.10) <0.001 0.02 (0.01 to 0.02) PARA2 2/518 (0.4) 11/959 (1.1) 0.36 (0.08 to 1.64) 0.187 · · · 0.48 (0.10 to 2.38) 0.368 · · · PARA3 37/518 (7.1) 21/959 (2.2) 3.46 (1.98 to 6.04) <0.001 0.05 (0.04 to 0.06) 5.10 (2.76 to 9.42) <0.001 0.06 (0.05 to 0.06) PARA4 10/518 (1.9) 14/959 (1.5) 1.36 (0.59 to 3.11) 0.466 · · · 1.98 (0.77 to 5.06) 0.156 · · · PJP 44/522 (8.4) 12/959 (1.3) 6.00 (3.12 to 11.54) <0.001 0.07 (0.06 to 0.08) 9.78 (4.77 to 20.05) <0.001 0.08 (0.07 to 0.08) PNEU 86/522 (16.5) 84/959 (8.8) 2.10 (1.51 to 2.91) <0.001 0.09 (0.06 to 0.11) 1.38 (0.91 to 2.11) 0.133 · · · PNEU (WB) 39/521 (7.5) 46/963 (4.8) 1.78 (1.13 to 2.79) 0.013 0.03 (0.01 to 0.05) 1.80 (1.04 to 3.15) 0.037 0.03 (0.00 to 0.05) PVEV 25/518 (4.8) 73/959 (7.6) 0.69 (0.43 to 1.10) 0.119 · · · 0.81 (0.46 to 1.43) 0.470 · · · RHINO 42/518 (8.1) 41/959 (4.3) 1.98 (1.27 to 3.11) 0.003 0.04 (0.02 to 0.06) 3.28

(1.95 to 5.51) <0.001 0.06 (0.04 to 0.07) RSV 152/518 (29.3) 30/959 (3.1) 12.82 (8.40 to 19.56) <0.001 0.27 (0.26 to 0.28) 20.58 (13.05 to 32.45) <0.001 0.28 (0.27 to 0.28) SASP 0/522 (0.0) 1/959 (0.1) · · · 0.970 · · · · · · 0.974 · · · SAUR 70/522 (13.4) 56/959 (5.8) 2.28 (1.56 to 3.32) <0.001 0.08 (0.05 to 0.09) 2.74 (1.75 to 4.28) <0.001 0.09 (0.06 to 0.10) a Cases – all children with radiologically-confirmed pneumonia; b Marginal odds ratios adjusted by age (in months) and season; c Conditional odds ratios adjusted by age (in months), season and all other pathogens. Highlighted rows reflect instances in which organism was significantly associated with case status. Site-specific density threshold cut-off values were used for the following organisms: adenovirus, human cytomegalovirus (NP/OP and whole blood), human bocavirus, H. influenzae type b and non-type b, pneumococcus (NP/OP and whole blood), M. catarrhalis, P. jirovecii, human rhinovirus and S. aureus (please refer to Table G.1 for cut-off densities which were applied). ADENO = adenovirus; BOPE = B. pertussis ; CI = confidence interval; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ; FA = 'fraction of association';

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus;

HIB = H. influenzae type b; HINF = non **-type** b **H. influenzae** 36

; HMPV = human metapneumovirus; MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type 2;** PARA3 = **parainfluenza virus type 3;** PARA4 = **parainfluenza virus type 4;** 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV = parechovirus/ enterovirus;

RHINO = human rhinovirus; RSV = respiratory syncytial virus; SASP = Salmonella spp.; **SAUR** = S. **aureus** 32

; WB = whole blood; Table produced using the stargazer package in R [66]. 123 4. Case-Control Analysis124 4.2.1All Children RSV (FA 0.28), non-typable H. influenzae (FA 0.14), S. aureus (FA 0.09), P. jirovecii (FA 0.08), adenovirus (FA 0.06), parainfluenza virus type 3 (FA 0.06), human rhinovirus (FA 0.06) and HMPV (FA 0.04) carriage in the upper respiratory tract were significantly associated with case status (Table 4.1). Other organisms significantly associated with case status (and together contributing to a combined FA of 0.15) included B. pertussis, influenza A and B, human bocavirus, H. influenzae type b, parainfluenza virus 1 and pneumococcus (as detected on whole blood) (Table 4.1). Focussing on the cases with radiologically-confirmed pneumonia assisted in diminishing the fraction of cases with no attributable cause of pneumonia: in the comparison of all cases to controls, the 'unknown aetiology' segment was 0.24, compared to 0.04 in the analysis of cases with radiologically-confirmed pneumonia compared to controls (Figure 4.5). In the combined cohort, P. jirovecii contributed the largest FA (0.35; 95% CI, 0.33 to 0.35) amongst children dying from pneumonia, and had an adjusted odds of 64.11 (95% CI, 18.93 to 217.09) in the conditional logistic regression analysis of being detected in cases dying in-hospital of pneumonia, compared to controls. Staphylococcus aureus (FA 0.22; 95% CI, 0.11 to 0.25), B. pertussis (FA 0.08;

95% CI, 0. 04 **to 0.** 08), adenovirus (FA **0.** 07; **95% CI, 0.** 03 **to 0.** 08) **and** RSV (FA **0.** 04; **95% CI, 0.** 01 **to 0.** 05) **were** also **significantly associated with** 57

in-hospital mortality in the South African cohort, overall (Figure 4.5). 4.2.2HEU Children In HEU children, RSV (FA 0.31), CMV (FA 0.16), non-type b H. influenzae (FA 0.13), S. aureus (FA 0.09), human rhinovirus (FA 0.08), adenovirus (FA 0.07), P. jirovecii (FA 0.06), influenza A (FA 0.04) and coronavirus NL63 (FA 0.03) detected on NP/OP swabs were associated with case status (Table 4.2), and the fraction of pneumonia attributed to no defined pathogen was 0.03 (Figure 4.5) (in the comparison between cases with radiologically-confirmed pneumonia (n=164) and controls (n=224)). No defined organism was associated with pneumonia when interrogating all HEU cases compared to controls in a substantial proportion (FA 0.36) of the cases in the analysis of all HEU cases compared to controls (Figure 4.5). Tab. 4.2: Marginal and

Conditional Odds Ratios of Organism Prevalence in NP/OP Swabs and Whole Blood (Radiologically-confirmed Pneumonia) – HEU Children Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** 3

ADENO 15/161 (9.3) 10/224 (4.5) 2.32 (1.00 to 5.40) 0.050 · · · 4.31 (1.53 to 12.15) 0.006 0.07 (0.03 to 0.09) BOPE 3/164 (1.8) 1/224 (0.4) 2.88 (0.29 to 28.53) 0.364 · · · 7.64 (0.62 to 94.73) 0.112 · · · CMV 47/161 (29.2) 37/224 (16.5) 1.78 (1.08 to 2.94) 0.024 0.13 (0.02 to 0.19) 2.26 (1.16 to 4.43) 0.017 0.16 (0.04 to 0.23) COR229 0/161 (0.0) 0/224 (0.0) · · · · · · · · · · · · · · · · · · COR43 3/161 (1.9) 17/224 (7.6) 0.21 (0.06 to 0.74) 0.015 · · · 0.28 (0.06 to 1.36) 0.113 · · · COR63 6/161 (3.7) 3/224 (1.3) 2.97 (0.69 to 12.79) 0.142 · · · 6.85 (1.29 to 36.33) 0.023 0.03 (0.01 to 0.04) CORHKU 6/161 (3.7) 3/224 (1.3) 3.36 (0.78 to 14.52) 0.103 · · · 1.87 (0.30 to 11.66) 0.504 · · · CPNEU 5/164 (3.0) 3/224 (1.3) 2.84 (0.63 to 12.83) 0.173 · · · 2.44 (0.38 to 15.75) 0.346 · · · FLUA 8/161 (5.0) 3/224 (1.3) 4.17 (1.04 to 16.66) 0.043 0.04 (0.00 to 0.05) 8.30 (1.70 to 40.58) 0.009 0.04 (0.02 to 0.05) FLUB 1/161 (0.6) 1/224 (0.4) 2.59 (0.11 to 59.87) 0.551 · · · 5.59 (0.23 to 137.26) 0.290 · · · FLUC 2/164 (1.2) 0/224 (0.0) · · · 0.982 · · · · · · 0.990 · · · HBOV 10/161 (6.2) 10/224 (4.5) 1.64 (0.64 to 4.18) 0.300 · · · 2.00 (0.61 to 6.55) 0.253 · · · HIB 2/164 (1.2) 1/224 (0.4) 3.58 (0.30 to 43.19) 0.314 · · · 8.92 (0.59 to 134.40) 0.113 · · · HINF 23/164 (14.0) 2/224 (0.9) 19.15 (4.29 to 85.44) <0.001 0.13 (0.11 to 0.14) 25.16 (4.42 to 143.12) <0.001 0.13 (0.11 to 0.14) HMPV 14/161 (8.7) 7/224 (3.1) 3.24 (1.21 to 8.66) 0.019 0.06 (0.02 to 0.08) 2.33 (0.65 to 8.35) 0.191 · · · MCAT 10/164 (6.1) 8/224 (3.6) 1.65 (0.63 to 4.37) 0.309 · · · 0.75 (0.20 to 2.92) 0.682 · · · Continued on next page . . . 125 Tab. 4.2, continued from previous page . . . Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-value** FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-value** FA **(95% CI)** MPNEU **1/** 161 (0.6) **2/** 224 **(0.** 9) 0 **.92** 462

(0.07 to 11.48) 0.949 · · · 0.66 (· · · to 179.78) 0.883 · · · PARA1 1/161 (0.6) 0/224 (0.0) · · · 0.979 · · · · · · 0.990 · · · PARA2 0/161 (0.0) 2/224 (0.9) · · · 0.981 · · · · · · 0.988 · · · PARA3 6/161 (3.7) 5/224 (2.2) 1.60 (0.47 to 5.49) 0.455 · · · 3.46 (0.79 to 15.15) 0.099 · · · PARA4 5/161 (3.1) 2/224 (0.9) 3.39 (0.63 to 18.13) 0.152 · · · 6.49 (0.77 to 54.77) 0.085 · · · PJP 11/164 (6.7) 2/224 (0.9) 6.03 (1.30 to 27.93) 0.021 0.06 (0.02 to 0.06) 6.25 (1.15 to 33.85) 0.033 0.06 (0.01 to 0.07) PNEU 10/164 (6.1) 5/224 (2.2) 3.93 (1.21 to 12.78) 0.022 0.05 (0.01 to 0.06) 2.45 (0.42 to 14.44) 0.320 · · · PNEU (WB) 11/163 (6.7) 8/225 (3.6) 2.31 (0.86 to 6.21) 0.095 · · · 2.59 (0.65 to 10.35) 0.177 · · · PVEV 12/161 (7.5) 19/224 (8.5) 1.01 (0.46 to 2.22) 0.974 · · · 1.29 (0.47 to 3.55) 0.617 · · · RHINO 17/161 (10.6) 13/224 (5.8) 2.16 (0.99 to 4.71) 0.054 · · · 3.77 (1.51 to 9.44) 0.004 0.08 (0.04 to 0.09) RSV 51/161 (31.7) 6/224 (2.7) 16.74 (6.73 to 41.64) <0.001 0.30 (0.27 to 0.31) 33.39 (12.13 to 91.91) <0.001 0.31 (0.29 to 0.31) SASP 0/164 (0.0) 0/224 (0.0) · SAUR 22/164 (13.4) 17/224 (7.6) 1.49 (0.74 to 2.98) 0.259 · · · 2.89 (1.18 to 7.07) 0.020 0.09 (0.02 to 0.12) a Cases – HEU children with radiologically-confirmed pneumonia; b Marginal odds ratios adjusted by age (in months) and season; c Conditional odds ratios adjusted by age (in months), season and all other pathogens. Highlighted rows reflect instances in which organism was significantly associated with case status. Site-specific density threshold cut-off values were used for the following organisms: adenovirus, human cytomegalovirus (NP/OP and whole blood), human bocavirus, H. influenzae type b and non-type b, pneumococcus (NP/OP and whole blood), M. catarrhalis, P. jirovecii, human rhinovirus and S. aureus (please refer to Table G.1 for cut-off densities which were applied). ADENO = adenovirus; BOPE = B. pertussis ; CI = confidence interval; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus; HEU = HIV-exposed, -uninfected;

HIB = H. influenzae type b; HINF = non **-type** b **H. influenzae** 36

; HMPV = human metapneumovirus; MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type 2;** PARA3 = **parainfluenza virus type 3;** PARA4 = **parainfluenza virus type 4;** 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV = parechovirus/ enterovirus;

RHINO = human rhinovirus; RSV = respiratory syncytial virus; SASP = Salmonella spp.; **SAUR** = S. **aureus** 32

; WB = whole blood; Table produced using the stargazer package in R [66]. 126 4. Case-Control Analysis127 The FA summed to >1.0 in the 'aetiology pie' describing the organisms associated with in-hospital mortality amongst HEU children: CMV (FA 0.61; 95% CI, 0.35 to 0.62), S. aureus (FA 0.37; 95% CI, 0.26 to 0.37), P. jirovecii (FA 0.25; 0.13 to 0.25) and coronavirus NL63 (FA 0.12; 95% CI, 0.08 to 0.12) were the four organisms associated with death in this group of children (Figure 4.5). 4.2.3HIV-unexposed Children RSV (FA 0.33), non-type b H. influenzae (FA 0.15), parainfluenza virus type 3 (FA 0.07), S. aureus (FA 0.06), adenovirus (FA 0.04), HMPV (FA 0.04), parainfluenza virus type 1 (FA 0.03) and P. jirovecii (FA 0.03) on NP/OP were associated with case status in HIV-unexposed children (n=245 cases with radiologically-confirmed pneumonia and available results; n=579 controls) (Table 4.3). Other organisms significantly associated with case status in the comparison between HIV-unexposed cases with radiologically-confirmed pneumonia and their controls included B. pertussis ,

influenza A and B and human bocavirus and 550

these together contributed to 0.08 of the FA in these children. The non-attributed fraction of pneumonia in the whole cohort of HIV-unexposed children (regardless of chest radiographic findings) was 0.38 (Figure 4.5). However, a substantially larger fraction with non-attributed pathogen association (0.65) was appreciated in the 'aetiology pie' of in-hospital mortality amongst HIV-unexposed children (Figure 4.5). Organisms significantly associated with in-hospital mortality in the HIV-unexposed group included P. jirovecii (FA 0.18;

95% CI, 0. 15 **to 0.** 18) **(aOR** 66.12; **95% CI,** 5.06 **to** 139

863.31) and adenovirus (FA 0.17;

95% CI, 0. 11 **to 0.** 18) **(aOR** 22.24; **95% CI,** 2.63 **to** 139

188.20) (Figure 4.5). 4.2.4HIV-infected Children A much narrower spectrum of organisms were associated with radiologically-confirmed pneumonia amongst HIV-infected children (n=89 cases with radiologically-confirmed pneumonia; n=136 controls), in whom only four organisms were associated with case-status and radiologically- confirmed pneumonia: CMV (FA 0.35), P. jirovecii (FA 0.23), RSV (FA 0.12) and parainfluenza virus type 3 (FA 0.10) (Table 4.4). Tab. 4.3: Marginal and Conditional Odds Ratios of Organism Prevalence in NP/OP Swabs and Whole Blood (Radiologically-confirmed Pneumonia) – HIV-unexposed Children Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** 3

ADENO 14/244 (5.7) 15/579 (2.6) 2.27 (1.07 to 4.81) 0.032 0.03 (0.00 to 0.05) 3.62 (1.56 to 8.42) 0.003 0.04 (0.02 to 0.05) BOPE 6/245 (2.4) 3/579 (0.5) 4.32 (1.05 to 17.80) 0.042 0.02 (0.00 to 0.02) 6.56 (1.44 to 29.91) 0.015 0.02 (0.01 to 0.02) CMV 56/244 (23.0) 160/579 (27.6) 0.68 (0.47 to 0.97) 0.035 · · · 0.75 (0.49 to 1.17) 0.207 · · · COR229 1/244 (0.4) 1/579 (0.2) 1.83 (0.11 to 29.76) 0.671 · · · 4.08 (0.19 to 89.70) 0.372 · · · COR43 7/244 (2.9) 27/579 (4.7) 0.53 (0.23 to 1.25) 0.148 · · · 0.81 (0.30 to 2.14) 0.665 · · · COR63 5/244 (2.0) 22/579 (3.8) 0.55 (0.20 to 1.51) 0.247 · · · 1.15 (0.39 to 3.38) 0.798 · · · CORHKU 3/244 (1.2) 14/579 (2.4) 0.50 (0.14 to 1.78) 0.283 · · · 0.69 (0.17 to 2.83) 0.608 · · · CPNEU 4/245 (1.6) 16/579 (2.8) 0.72 (0.23 to 2.25) 0.568 · · · 0.33 (0.07 to 1.50) 0.151 · · · FLUA 8/244 (3.3) 10/579 (1.7) 2.24 (0.82 to 6.07) 0.114 · · · 3.57 (1.20 to 10.63) 0.022 0.02 (0.01 to 0.03) FLUB 5/244 (2.0) 2/579 (0.3) 9.50 (1.71 to 52.72) 0.010 0.02 (0.01 to 0.02) 6.97 (1.09 to 44.60) 0.040 0.02 (0.00 to 0.02) FLUC 3/245 (1.2) 6/579 (1.0) 1.21 (0.30 to 4.94) 0.793 · · · 1.47 (0.24 to 8.91) 0.676 · · · HBOV 6/243 (2.5) 4/579 (0.7) 3.61 (0.99 to 13.18) 0.052 · · · 5.42 (1.10 to 26.69) 0.038 0.02 (0.00 to 0.02) HIB 2/245 (0.8) 0/579 (0.0) · · · 0.969 · · · · · 0.974 · · · HINF 59/245 (24.1) 55/579 (9.5) 2.98 (1.98 to 4.49) <0.001 0.16 (0.12 to 0.19) 2.56 (1.55 to 4.22) <0.001 0.15 (0.09 to 0.18) HMPV 16/243 (6.6) 19/579 (3.3) 2.13 (1.06 to 4.28) 0.034 0.03 (0.00 to 0.05) 2.83 (1.28 to 6.24) 0.010 0.04 (0.01 to 0.06) MCAT 23/245 (9.4) 37/579 (6.4) 1.40 (0.80 to 2.42) 0.237 · · · 1.29 (0.65 to 2.56) 0.462 · · · Continued on next page . . . 128 Tab. 4.3, continued from previous page . . . Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** 3

MPNEU 1/243 (0.4) 3/579 (0.5) 0.91 (0.09 to 9.21) 0.934 · · · 3.60 (0.30 to 42.71) 0.310 · · · PARA1 8/243 (3.3) 2/579 (0.3) 11.12 (2.28 to 54.19) 0.003 0.03 (0.02 to 0.03) 21.71 (4.17 to 113.12) <0.001 0.03 (0.03 to 0.03) PARA2 1/244 (0.4) 6/579 (1.0) 0.43 (0.05 to 3.66) 0.442 · · · 0.73 (0.08 to 6.61) 0.777 · · · PARA3 19/244 (7.8) 11/579 (1.9) 4.78 (2.19 to 10.42) <0.001 0.06 (0.04 to 0.07) 7.81 (3.34 to 18.23) <0.001 0.07 (0.05 to 0.07) PARA4 4/244 (1.6) 10/579 (1.7) 0.97 (0.30 to 3.17) 0.956 · · · 1.19 (0.32 to 4.39) 0.793 · · · PJP 10/245 (4.1) 8/579 (1.4) 2.51 (0.96 to 6.53) 0.060 · · · 3.95 (1.26 to 12.43) 0.019 0.03 (0.01 to 0.04) PNEU 30/245 (12.2) 38/579 (6.6) 1.73 (1.03 to 2.89) 0.037 0.05 (0.00 to 0.08) 1.22 (0.63 to 2.35) 0.563 · · · PNEU (WB) 19/245 (7.8) 34/583 (5.8) 1.38 (0.76 to 2.52) 0.288 · · · 1.59 (0.77 to 3.32) 0.212 · · · PVEV 11/244 (4.5) 42/579 (7.3) 0.69 (0.35 to 1.38) 0.295 · · · 0.61 (0.26 to 1.40) 0.241 · · · RHINO 8/244 (3.3) 14/579 (2.4) 1.29 (0.53 to 3.16) 0.572 · · · 2.41 (0.85 to 6.79) 0.097 · · · RSV 84/244 (34.4) 21/579 (3.6) 13.54 (8.01 to 22.89) <0.001 0.32 (0.30 to 0.33) 17.88 (10.18 to 31.39) <0.001 0.33 (0.31 to 0.33) SASP 0/245 (0.0) 0/579 (0.0) · · · · · · · · · · · · · · · · · · SAUR 25/245 (10.2) 30/579 (5.2) 2.02 (1.14 to 3.57) 0.016 0.05 (0.01 to 0.07) 2.60 (1.33 to 5.08) 0.005 0.06 (0.03 to 0.08) a Cases – HIV-unexposed children with radiologically-confirmed pneumonia; b Marginal odds ratios adjusted by age (in months) and season; c Conditional odds ratios adjusted by age (in months), season and all other pathogens. Highlighted rows reflect instances in which organism was significantly associated with case status. Site-specific density threshold cut-off values were used for the following organisms: adenovirus, human cytomegalovirus (NP/OP and whole blood), human bocavirus, H. influenzae type b and non-type b, pneumococcus (NP/OP and whole blood), M. catarrhalis, P. jirovecii, human rhinovirus and S. aureus (please refer to Table G.1 for cut-off densities which were applied). ADENO = adenovirus; BOPE = B. pertussis ; CI = confidence interval; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus;

HIB = H. influenzae type b; HINF = non **-type** b **H. influenzae** 36

; HMPV = human metapneumovirus; MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type 2;** PARA3 = **parainfluenza virus type 3;** PARA4 = **parainfluenza virus type 4;** 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV = parechovirus/ enterovirus;

RHINO = human rhinovirus; RSV = respiratory syncytial virus; SASP = Salmonella spp.; **SAUR** = S. **aureus** 32

; WB = whole blood; Table produced using the stargazer package in R [66]. 129 Tab. 4.4: Marginal and Conditional Odds Ratios of Organism Prevalence in NP/OP Swabs and Whole Blood (Radiologically-confirmed Pneumonia) – HIV-infected Children Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** 3

ADENO 7/89 (7.9) 4/136 (2.9) 2.65 (0.73 to 9.59) 0.136 · · · 1.68 (0.27 to 10.40) 0.576 · · · BOPE 1/89 (1.1) 0/136 (0.0) · · · 0.987 · · · · · · 0.996 · · · CMV 41/89 (46.1) 25/136 (18.4) 3.99 (2.06 to 7.72) <0.001 0.35 (0.24 to 0.40) 4.02 (1.60 to 10.11) 0.003 0.35 (0.17 to 0.42) COR229 0/89 (0.0) 0/136 (0.0) · COR43 3/89 (3.4) 9/136 (6.6) 0.47 (0.12 to 1.84) 0.273 · · · 0.84 (0.10 to 6.75) 0.865 · · · COR63 2/89 (2.2) 1/136 (0.7) 4.11 (0.35 to 48.03) 0.257 · · · 2.00 (0.12 to 33.95) 0.629 · · · CORHKU 0/89 (0.0) 5/136 (3.7) · · · 0.988 · · · · · · 0.990 · · · CPNEU 0/89 (0.0) 0/136 (0.0) · · · · · · · · · · · · · · · · · · FLUA 1/89 (1.1) 0/136 (0.0) · · · 0.986 · · · · · · 0.996 · · · FLUB 0/89 (0.0) 0/136 (0.0) · · · · · · · · · · · · · · · · · · FLUC 1/89 (1.1) 1/136 (0.7) 1.86 (0.10 to 35.50) 0.679 · · · 0.69 (0.02 to 19.17) 0.824 · · · HBOV 11/89 (12.4) 7/136 (5.1) 2.91 (1.05 to 8.01) 0.038 0.08 (0.01 to 0.11) 4.25 (0.91 to 19.81) 0.064 · · · HIB 1/89 (1.1) 0/136 (0.0) · · · 0.987 · · · · · · 0.997 · · · HINF 27/89 (30.3) 13/136 (9.6) 4.34 (2.06 to 9.16) <0.001 0.23 (0.16 to 0.27) 2.05 (0.72 to 5.85) 0.177 · · · HMPV 4/89 (4.5) 3/136 (2.2) 2.17 (0.46 to 10.30) 0.326 · · · 1.37 (0.14 to

13.03) 0.781 · · · MCAT 21/89 (23.6) 9/136 (6.6) 4.28 (1.83 to 9.98) 0.001 0.18 (0.11 to 0.21) 2.04 (0.62 to 6.76) 0.240 · · · Continued on next page . . . 130 Tab. 4.4, continued from previous page . . . Organism CasesaControls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** 3

MPNEU 0/89 (0.0) 1/136 (0.7) · · · 0.988 · · · · · · 1.000 · · · PARA1 3/89 (3.4) 3/136 (2.2) 1.54 (0.29 to 8.24) 0.609 · · · 1.09 (0.10 to 12.24) 0.947 · · · PARA2 1/89 (1.1) 3/136 (2.2) 0.50 (0.05 to 5.04) 0.554 · · · 0.63 (0.04 to 9.01) 0.729 · · · PARA3 11/89 (12.4) 4/136 (2.9) 4.58 (1.33 to 15.75) 0.015 0.10 (0.03 to 0.12) 4.59 (1.00 to 20.99) 0.048 0.10 (0.00 to 0.12) PARA4 1/89 (1.1) 2/136 (1.5) 0.75 (0.06 to 8.75) 0.819 · · · 1.74 (0.11 to 27.29) 0.691 · · · PJP 21/89 (23.6) 2/136 (1.5) 21.47 (4.71 to 97.92) <0.001 0.22 (0.19 to 0.23) 43.08 (7.99 to 232.23) <0.001 0.23 (0.21 to 0.23) PNEU 30/89 (33.7) 31/136 (22.8) 1.87 (1.01 to 3.47) 0.045 0.16 (0.00 to 0.24) 1.12 (0.42 to 2.98) 0.814 · · · PNEU (WB) 9/89 (10.1) 4/136 (2.9) 4.62 (1.29 to 16.54) 0.018 0.08 (0.02 to 0.10) 2.79 (0.53 to 14.79) 0.225 · · · PVEV 2/89 (2.2) 11/136 (8.1) 0.28 (0.06 to 1.30) 0.102 · · · 0.71 (0.12 to 4.29) 0.709 · · · RHINO 12/89 (13.5) 13/136 (9.6) 1.40 (0.60 to 3.27) 0.435 · · · 3.12 (0.93 to 10.48) 0.064 · · · RSV 11/89 (12.4) 3/136 (2.2) 7.55 (1.94 to 29.43) 0.003 0.11 (0.06 to 0.12) 37.80 (5.31 to 268.85) <0.001 0.12 (0.10 to 0.12) SASP 0/89 (0.0) 1/136 (0.7) · · · 0.987 · · · · · · 0.997 · · · SAUR 17/89 (19.1) 7/136 (5.1) 4.39 (1.70 to 11.33) 0.002 0.15 (0.08 to 0.17) 2.74 (0.72 to 10.45) 0.137 · · · a Cases – HIV-infected children with radiologically-confirmed pneumonia; b Marginal odds ratios adjusted by age (in months) and season; c Conditional odds ratios adjusted by age (in months), season and all other pathogens. Highlighted rows reflect instances in which organism was significantly associated with case status. Site-specific density threshold cut-off values were used for the following organisms: adenovirus, human cytomegalovirus (NP/OP and whole blood), human bocavirus, H. influenzae type b and non-type b, pneumococcus (NP/OP and whole blood), M. catarrhalis, P. jirovecii, human rhinovirus and S. aureus (please refer to Table G.1 for cut-off densities which were applied). ADENO = adenovirus; BOPE = B. pertussis ; CI = confidence interval; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus; HEU = HIV-exposed, -uninfected;

HIB = H. influenzae type b; HINF = non **-type** b **H. influenzae** 36

; HMPV = human metapneumovirus; MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type 2;** PARA3 = **parainfluenza virus type 3;** PARA4 = **parainfluenza virus type 4;** 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; PVEV = parechovirus/ enterovirus;

RHINO = human rhinovirus; RSV = respiratory syncytial virus; SASP = Salmonella spp.; **SAUR** = S. **aureus** 32

; WB = whole blood; Table produced using the stargazer package in R [66]. 131 All cases compared to controls Radiologically- confirmed pneumonia compared to controls In-hospital death compared to controls 2524 4 28424 n=917n=52235 n=37 All 25% 24% 6% 28% 15%4 4% 6% 35% 24% 4% children 10% 3% 6 4% 34% 14% 6%6 7%4 108% 8 7%5% 4%4 4 149% 8% 6%6 6 22% 8%7 8 75 4 26 n36=29731 93 38 4 3%3%4% 6 n=164 228.9 8.9% 1n8.=5 8 HEU 26% 10% 108% 36% 4%3% 31% 16% 6%7 7% 8% 8 9% 13% 45.2 45.2% 18.5% 27.4% 8% 5%9 84 316 8513 17 28 27.4 18 HIV- 28% 38% n=464 38 33 33% 17% n=24518%n=11 8 8% 3% unexposed 11% 2% 15% 3% 317 34% 4% 65% 65 115%4%4%3%3%2% 2 7%6%4 4 5 44 27 3 3 2 20 15 n=11535 76 20 n=89n=17 HIV- infected 27% 25% 20% 10% 10 18% 35% 23% 20% 10% 10 12% 52% 52 48 48% 12 2518 23 ADENO CMV FLUA HMPV PJP RSV Other BOPE COR63 HINF PARA3 RHINO SAUR No attrib. Fig. 4.5: Pneumonia 'Aetiology Pies' Stratified by HIV-infection & -Exposure Status: Overall, Radiologically-confirmed Pneumonia & In-hospital Mor- tality ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR63 = coronavirus NL63; FLUA =

influenza A; HINF = non-type b H. influenzae ; HMPV = human metapneumovirus; No attrib. = no attribution; PARA3 = parainfluenza virus 3 (= parainfluenza virus 1); PJP = P. jirovecii ; RHINO = human rhinovirus; RSV = respiratory syncytial virus; SAUR = S. aureus. 'n' refers to the number of cases available in each analysis. Non-type b H. influenzae featured prominently in the 'aetiology pie' for pneumonia

in HIV- infected children, regardless **of** chest radiographic findings, **in** the **South African** **874**

PERCH cohort (FA 0.18;

95% CI, 0. 01 **to 0.** 25) **(aOR** 2.62; **95% CI,** 1.03 **to** **139**

6.65) (Figure 4.5), whereas S. aureus was associated with case status in the sub-set of HIV-infected children with hypoxic pneumonia (FA 0.15;

95% CI, 0. 02 **to 0.** 18) **(aOR** 4.55; **95% CI,** 1.13 **to** **139**

18.28) (data not shown). The only organism associated with in-hospital mortality amongst HIV-infected children was P. jirovecii (FA 0.52;

95% CI, 0. 46 **to 0.** 53) **(aOR** 89.19; **95% CI,** 7.15 **to 1** **139**

112.09; P<0.001) (Figure 4.5). Stratification by ART access

in HIV-infected children In **HIV-infected children** on ART **at** the time **of** **163**

enrolment into PERCH (24 cases and 113 controls), the only pathogen significantly associated with case status in those with radiologically- confirmed pneumonia was RSV (aOR 69.96; 95% CI, 4.14 to 1 181.87), P=0.003 and the FA attributable to RSV was 0.21 (95% CI, 0.16 to 0.21) 1. In contrast, amongst children not on ART at time of enrolment into PERCH (61 cases versus 23 controls), P. jirovecii was the only pathogen associated with case status in HIV-infected children with radiologically-confirmed pneumonia (aOR 11.69;

95% CI 1.22 to 111.91), **P=0.** 029. The FA **associated with** **71**

P. jirovecii was 0.27 (95% CI, 0.05 to 0.29) 2. 4.2.5Organism Category Summary Association with Case Status Summary estimates of the association of organism categories with case status were possible by pooling all bacterial organisms into a 'bacterial' group, all viral organisms except CMV into a 'respiratory viral' group, setting P. jirovecii and CMV into an 'opportunistic pathogens' group and assigning a 'non-attributed' group where the FA analysis failed to identify any organism associated with case status. In the combined group (all children, regardless of HIV-infection or -exposure status), respiratory viruses were associated with an FA of 0.59 (95% CI, 0.47 to 0.62) of pneumonia in cases with radiologically-confirmed disease, bacteria were associated with 0.29 (95% CI, 0.18 to 0.35), opportunistic pathogens with 0.08 (95% CI, 0.07 to 0.08) and no 1 In this analysis, 5 (20.8%) of the 24 cases were positive for RSV, compared to 3 (2.7%) of the 113 controls, and the power of the analysis was 0.83.

Median time on ART was 13.8 weeks **(IQR,** 4.9 **to** 37 **.4** **962**

weeks) in cases and 23.1 weeks (IQR, 6.6 to 53.0 weeks) in controls; P=0.218. 2 In this analysis, 18 (29.5%) of the 61 cases were positive for P. jirovecii, compared to 2 (8.7%) of the 23 controls, and the power of the analysis was 0.63. attribution was made in 0.04 (95% CI, -0.05 to 0.28). The largest contributor to death in the combined group of children (regardless of HIV-infection or -exposure status) was the opportunistic group (FA 0.35; 95% CI, 0.33 to 0.35) (which consisted only of P. jirovecii in this analysis), followed by bacteria (FA 0.30;

95% CI, 0. 15 **to 0.** 33) **and** respiratory viruses (FA **0.** 11; **95% CI, 0.** 04 **to 0.** 13). **Figure** **369**

4.6 summarises these associations in HEU, HIV-unexposed and HIV-infected children. In HEU and HIV-unexposed children, the respiratory viral pathogens predominated as being associated with case status regardless of chest radiographic changes (FA 0.42

(95% CI, 0. 32 **to 0.** 47) **and** FA **0.** 43 **(95% CI, 0.** 33 **to 0.** 49), **respectively), and** especially so in **the** 584

sub-group of cases with radiologically-confirmed pneumonia (FA 0.53

(95% CI, 0. 39 **to 0.** 58) **and** FA **0.** 57 **(95% CI, 0.** 43 **to 0.** 61), respectively). In **HIV-** 14

infected children, opportunistic pathogens predominated regardless of chest radiographic findings (FA 0.52; 95% CI, 0.31 to 0.60) and in children with radiologically-confirmed pneumonia (FA 0.58; 95% CI, 0.38 to 0.65). The non-attributed group tended to decrease in all groups when interrogating the association between case status with radiologically-confirmed pneumonia compared to the control group. The opportunistic pathogens were identified as being associated with in-hospital mortality in all three groups (FA 0.64

(95% CI, 0. 44 **to 0.** 80), FA **0.** 18 **(95% CI, 0.** 15 **to 0.** 18) **and** FA **0.** 52 **(95% CI, 0.** 46 **to 0.53)** 390

for HEU, HIV-unexposed and HIV-infected, respectively) (Figure 4.6). The only group in which bacterial species

were significantly associated with in-hospital mortality, 71

was the HEU group (FA 0.27; 95% CI, 0.24 to 0.34) (Figure 4.6), this being solely due to S. aureus (Figure 4.5). Stratification by ART access in HIV-infected children As seen on page 133, access to ART played a role in shifting the pathogen spectrum

in HIV-infected children. In **HIV-infected children** on ART **at** the time **of** 163

enrolment into the study, opportunistic infections (consisting only of CMV) and respiratory viruses (consisting only of RSV) were associated with case status, regardless of chest radiographic findings (FA 0.29

(95% CI, 0. 02 **to 0.** 35) **and 0.** 18 **(95% CI, 0.14 to 0.** 18), **respectively).** 605

Respiratory viruses (consisting only of RSV) were associated with case status with radiologically-confirmed pneumonia

in HIV-infected children accessing ART **at the time of** 886

enrolment into PERCH (FA 0.21; 95% CI, 0.16 to 0.21). No aetiologic group attribution could be made for children dying in-hospital (n=6). (a) (b) (c) BacteriaVirusesOppor. No attrib. Fig. 4.6: Summary of Organism Types

Associated with Pneumonia in (a) HEU, (b) **HIV-** unexposed **and** (c) **HIV-** infected **Children** 242

CI = confidence interval;

HEU = HIV-exposed, -uninfected; HIV = human immunodeficiency virus type 1; 461

No attrib. = no attribution; Oppor. = opportunistic pathogens (human cytomega- lovirus (CMV) and P. jirovecii). Amongst HIV-infected not on ART at PERCH enrolment, the opportunistic pathogen group (consisting only of P. jirovecii) was associated with case status regardless of chest radiographic findings (FA 0.32; 95% CI, 0.18 to 0.34) and in those with radiologically-confirmed pneumonia (FA 0.27; 95% CI, 0.05 to 0.29), but no firm attribution could be assigned to in-hospital mortality (n=10; FA 1.00; 95% CI, 1.00 to 1.00). 4.2.6Pneumonia Aetiology Associations in HIV-uninfected Children as a Combined Group The case-control analyses presented above were stratified by HIV-infection and -exposure status, and have not presented summary results for the combined HIV-uninfected group. This was so as to highlight the differences in organism association with case status

between HEU and HIV- unexposed children. 391

The former group of children (HEU) tended to have significant associations of radiologically-confirmed pneumonia and in-hospital mortality with opportunistic pathogens (CMV and P. jirovecii), which was not as striking in the HIV-unexposed group and would have been obscured if focus had been drawn to the HIV-uninfected group as a whole. The 'top five' organisms associated with radiologically-confirmed pneumonia in HIV-uninfected children (regardless of HIV-exposure status) included: RSV (aOR 0.31; 95% CI, 0.30 to 0.32), non-type b H. influenzae (aOR 0.13; 95% CI, 0.09 to 0.16), S. aureus

(aOR 0. 07; 95% CI, 0. 04 to 0. 09), adenovirus (aOR 0. 06; 95% CI, 0. 04 to 0. 06) and 62

parainfluenza virus type 3

(aOR 0. 05; 95% CI, 0. 04 to 0. 05). Pneumocystis jirovecii (aOR 0. 19; 95% CI, 0. 16 to 0. 62

20), S. aureus

(aOR 0. 16; 95% CI, 0. 03 to 0. 19), B. pertussis (aOR 0. 322

14;

95% CI, 0. 05 to 0. 15), HMPV (aOR 0. 12; 95% CI, 0. 00 to 0. 14), adenovirus (aOR 0. 09; 95% CI, 0.02 to 0. 10) and RSV (aOR 0. 09; 95% CI, 0. 04 to 0. 10) were 59

associated with in-hospital mortality in the combined group of HIV-uninfected children. Respiratory viruses were associated with case status in 0.61 (95% CI, 0.50 to 0.66) of HIV- uninfected cases with radiologically-confirmed pneumonia, bacteria with 0.23 (95% CI, 0.14 to 0.28) and opportunistic pathogens (solely attributed to P. jirovecii) with 0.04

(95% CI, 0. 03 to 0. 05). In HIV- uninfected children 29

that died in-hospital, bacteria (FA 0.30;

95% CI, 0. 08 to 0. 34) and respiratory viruses (FA 0. 30; 95% CI, 0. 07 to 261

0.34) contributed equally to the 'aetiology pie' in HIV-uninfected children, and the opportunistic pathogens group (solely attributed by P. jirovecii) contributed to 0.19 (95% CI, 0.16 to 0.20) of in-hospital deaths. 4.2.7Age Group Stratifications Figures 4.7 and 4.8 present the age-group stratified 'aetiology pies' for pneumonia for the South African PERCH cohort in

children <12 months of age and ≥12 months of age, 144

respectively. Immediately apparent from a comparison of the 'aetiology pies' presented here, is the relative lack of association of organism NP/OP carriage and pneumonia case status in children ≥12 months of age which likely springs from the lack of statistical power to detect significant associations in this age group. At the PERCH South African site, 25.3% (204/805) of the HIV-uninfected cases and 27.8% (32/115) of the HIV-infected cases were ≥12 months of age (Tables 3.1 and 3.3). Associations with

pneumonia in children<12 months of age In the 526

analysis of the combined cohort of children <12 months

of age with radiologically-confirmed pneumonia compared to controls, 153

RSV (FA 0.34; 95% CI, 0.33 to 0.34) detected on NP/OP swabs was the organism most prominently associated with case status (aOR 35.78; 95% CI, 19.88 to 64.40). Non-type b H. influenzae (FA 0.16; 95%

CI, 0.13 to 0.19), P. jirovecii (FA 0.10; 95% CI, 0.09 to 0.11) and S. aureus (FA 0.08; 95% CI, 0.03 to 0.11) contributed a further 0.34 combined FA to the 'aetiology pie' in children <12 months (Figure 4.7). 'Other' organisms associated with radiologically-confirmed pneumonia in children <12 months of age included: B. pertussis (FA 0.02; 95% CI, 0.01 to 0.03), human bocavirus (FA 0.02; 95% CI, 0.01 to 0.03) and parainfluenza virus 1 (FA 0.01;

95% CI, 0. 00 to 0. 02). Organisms associated with in-hospital mortality 845

in the combined group of children <12 months of age included: P. jirovecii (FA 0.41; 95% CI, 0.40 to 0.42), S. aureus (FA 0.23; 95% CI, 0.08 to 0.27), parainfluenza virus 1 (FA 0.12; 95% CI, 0.01 to 0.13), B. pertussis (FA 0.09;

95% CI, 0. 04 to 0. 10) and RSV (FA 0. 06; 95% CI, 0. 02 to 0. 06) (Figure 369

4.7). A similar spectrum of organisms detected on NP/OP swab PCR

were associated with radiologically- confirmed pneumonia in 472

HEU

and HIV- unexposed children<12 months of age, with RSV and non- 885

type b H. influenzae being the first and second most prominent organisms in the 'aetiology pies' for these groups of children (Figure 4.7). 'Other' organisms associated with radiologically- confirmed pneumonia in HEU children <12 months of age included human bocavirus (FA 0.06;

95% CI, 0. 02 to 0. 07) and coronavirus NL63 (FA 0. 04; 95% CI, 0. 01 to 0. 05). In HIV- 14

unexposed children <12 months of age, 'other' organisms associated with radiologically-confirmed pneumonia included B. pertussis (FA 0.03; 95% CI, 0.01 to 0.03) and parainfluenza virus 1 (FA 0.02; 95% CI, 0.02 to 0.02). All cases compared to controls Radiologically- confirmed pneumonia compared to controls 4 In-hospital death compared to controls 9 20 29n=68134 6 4%6% 4 5n=390 6 9%n=31 All 29% 20% 5 5% 3% 34% 4% 5%6 6% 41 41% 6%9 9% children 12% 12 4% 3 5%4 9% 8%5%5 5 16% 10% 7% 8%7 8 23% 12% 12 9 30 30% 8 30% 3n0=233 16 36 36% 10 28% 28 n=131 36.3 36.3% 238.9 8.9% 8.9% 8.9 n=7 HEU 11% 4% 6%4 12% 10% 27.4% 18.5% 18.5 117% 6%6%6 7% 7 766 1277 16 27.4 24 32 HIV- unexposed 32% 35% n35=333 40 40% 16% 5% 4% 4% n5=177n=8 424% 13% 13 4% 6%6%4%4 4 19% 5%4 7%5 7 76% 76 6619 29 11.9 HIV- 33 33% 29% n=83 37.3 37.3% 11.9% n=62n=15 23.7 infected 26% 26 12% 12 23.7% 27.1% 27.1 50.850.8% 49.2% 49.2 ADENO BOPE CMV COR63 HINF HMPV PARA1 PARA3 PJP RHINO RSV SAUR Other No attrib. Fig. 4.7: Pneumonia 'Aetiology Pies' for Children <12 Months of Age Stratified by HIV-infection & -Exposure Status: Overall, Radiologically-confirmed Pneumonia & In-hospital Mortality ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR63 = coronavirus NL63; HINF = non-type b H. influenzae ; HMPV = human metapneumovirus; No attrib. = no attribution; PARA1 = parainfluenza virus 1; PARA3 = parainfluenza virus 3; PJP = P. jirovecii ; RHINO = human rhinovirus; RSV = respiratory syncytial virus; SAUR = S. aureus. 'n' refers to the number of cases avail- able in each analysis. Amongst HEU children <12 months of age, CMV detected on NP/OP swabs above cut-off densities which best distinguished between cases and controls was the organism most prominently

associated with in-hospital mortality (FA 0. 57; 95% CI, 0. 934

18 to 0.57). Staphylococcus aureus (FA 0.43; 95% CI, 0.29 to 0.43), P. jirovecii (FA 0.29;

95% CI, 0. 12 to 0.29), coronavirus NL63 (FA 0. 14; 95% CI, 0. 10 to 0. 14) and RSV (FA 0. 14; 95% CI, 0. 10 to 0. 343

14) were also associated with in-hospital mortality in this group of children (Figure 4.7). Pneumocystis jirovecii was the only organism associated with in-hospital mortality amongst HIV-unexposed children <12

months of age (FA 0. 24; 95% CI, 0. 16 to 0. 100

25) (Figure 4.7). In HIV-infected children <12

months of age, CMV (FA 0. 44; 95% CI, 0. 18 to 0. 100

52), P. jirovecii (FA 0.32; 95% CI, 0.29 to 0.32), non-type b H. influenzae (FA 0.28;

95% CI, 0. 15 to 0. 30) and RSV (FA 0. 14; 95% CI, 0. 13 to 0. 15) were the four organisms associated with 57

case status in the group of children with radiologically-confirmed pneumonia (Figure 4.7). Pneumocystis jirovecii (FA 0.60;

95% CI, 0. 56 to 0. 60) and CMV (FA 0. 58; 95% CI, 0. 24 to 0. 60) were the two organisms significantly associated with 57

in-hospital mortality amongst HIV-infected pneumonia cases <12 months of age (Figure 4.7). Associations with pneumonia

in children ≥12 months of age As mentioned above, in the analysis of 778

children ≥12 months of age, a large proportion of the 'aetiology pies' derived through the attributable fraction analyses were assigned to no defined aetiologic association, particularly so in the analysis of all cases compared to controls, and cases who died in-hospital compared to controls (Figure 4.8). Striking in the 'aetiology pies' for the ≥12 months age group, however, is that adenovirus (FA 0.33; 95% CI, 0.23 to 0.33) and HMPV (FA 0.33; 95% CI, 0.21 to 0.33) were the only two pathogens significantly associated with case status in those that died in-hospital. Furthermore, amongst HEU children with radiologically-confirmed pneumonia, pneumococcus (identified through lytA PCR on whole blood specimens) was the organism most associated with cases status (FA 0.15; 95% CI, 0.05 to 0.16) (Figure 4.8). Human rhinovirus (FA 0.14; 95% CI, 0.07 to 0.15), influenza A (FA 0.12;

95% CI, 0. 05 to 0. 12) and RSV (FA 0. 09; 95% CI, 0. 01 to 0. 09) were also significantly associated with 57

cases status in HEU children ≥12 months of age with

radiologically-confirmed pneumonia. All cases compared to controls Radiologically- confirmed pneumonia 585

compared to controls In-hospital death compared to controls All children 12 7 67% 6% 5% 55% 12% 62% n=236 10 910% 9% 8 8% 7% 44% n=132 44 33 33% 34% 34n=6 53b 3 77% 76%5%4% 33% HEU 17 17% 9 9% 9% 9 65% n=64 65 6 515 15% 14 14% 12% 4 50% 33 n=33n=1 50 100% 129% 1514 9 100 HIV-unexposed 15% n=131 6 66% 6% 6% 14% 48% n=68n=3 48 85% 66% 65%5%4% 100% 855 54 25 100 HIV- infected 100% n=32n=27n=2 25% 750% 100 75 100 ADENO COR63 HBOV MCAT PARA3 RHINO SAUR CMV FLUA HMPV PARA1 PNEU RSV No attrib. Fig. 4.8: Pneumonia 'Aetiology Pies' for Children ≥12 Months of Age Stratified by HIV-infection & -Exposure Status: Overall, Radiologically-confirmed Pneumonia & In-hospital Mortality ADENO = adenovirus; CMV = human cytomegalovirus; COR63 = coronavirus NL63; FLUA =

influenza A; HBOV = human bocavirus; HMPV = human metapneumovirus; 370

MCAT = M. catarrhalis ; No attrib. = no attribution; PARA1 = parainfluenza virus 1; PARA3 = parainfluenza virus 3; PNEU = S. pneumoniae (detected on whole blood PCR); RHINO = human rhinovirus; RSV = respiratory syncytial virus; SAUR = S. aureus. 'n' refers to the number of cases available in each analysis. HIV-unexposed children ≥12 months of age who had radiologically-confirmed pneumonia, had a wider spectrum of (predominantly viral) organisms associated with case status: viruses contributed FA 0.40 (95% CI, 0.14 to 0.44) to the 'aetiology pie', whilst S. aureus (FA 0.06; 95% CI, 0.03 to 0.06) and M. catarrhalis (FA 0.06; 95% CI, 0.00 to 0.07) were the only bacterial organisms associated with case status in this analysis (Figure 4.8). In

HIV-infected children ≥12 months of age with radiologically-confirmed pneumonia, 554

CMV (FA 0.25; 95% CI, 0.08 to 0.26) was the only organism that, if detected on NP/OP swabs in densities greater than the cut-off density that best distinguished between cases and controls, was significantly associated with case status (Figure 4.8). 4.2.8Stratification by Pneumonia Severity A further

analysis was conducted in order to interrogate **the** associations **of** 59

pathogen profiles detected on NP/OP swabs and whole blood (for lytA), stratified by pneumonia severity (using the WHO pre-2012 classification) and these are presented in Figures 4.9 and 4.10. The most interesting outcome of the analysis of pneumonia aetiology (inferred by the association of organisms detected on NP/OP swab of PCR of whole blood (for lytA)) when stratifying by pneumonia severity, was that P. jirovecii predominated in the 'aetiology pies' for in-hospital mortality overall (FA 0.52;

95% CI, 0. 50 **to 0.** 53), **and in** the **HIV-infected** group (FA **0.** 72; **95% CI, 0.** 63 **to 0.** 29

73) in children with WHO-defined severe pneumonia (Figure 4.9), whereas there was a shift towards predominance of CMV being associated with

in-hospital mortality amongst **children with** very **severe pneumonia in** 72

the HEU group (FA 0.59; 95% CI, 0.24 to 0.60) (Figure 4.10). There was insufficient statistical power to determine aetiologic associations with in-hospital

mortality in HIV-infected children with very severe **pneumonia.** 624

Pneumococcus (detected by lytA PCR of whole blood) was associated with case status in FA 0.04 (95% CI, 0.01 to 0.05) of children with severe pneumonia that had radiologically-confirmed pneumonia (Figure 4.9). Staphylococcus aureus was prominently associated with in-hospital mortality in the very severe pneumonia group overall (FA 0.31,

95% CI, 0. 25 **to 0.** 33) **and in** HEU **children** (FA **0.** 40, **95% CI, 0.** 17 **to 0.** 29

40) (Figure 4.10). All cases compared to controls Radiologically- confirmed pneumonia compared to controls In-hospital death compared to controls 2427 3n2=621 13 13% n=343n=19 All children 24% 8% 32% 27% 15 15% 4% 52% 52 38 38% 88%8% 10% 108% 4%4 6% 10% 87%5%4%4%8 7% 6%4 6 HEU 7 24 24% 54 4 52% n=198 8 7 31 31% 6 35% 10 n35=101n=3 10% 106% 5% 52 9%5% 8%5% 100% 63% 5 3 27 97%5 875 25 100 HIV- unexposed 27% 39% n=320 39 32 32% 25% 4% n=166n=4 9%3% 4 4% 100% 97%2% 10% 4%3 5%4%4%3% 72 7% 6%5%4 104 544 3 28 76 5 22 100 28 n=76n=61n=11 HIV- infected 28% 7% 7 65% 65 22% 9% 9 69% 69 72% 72 28% ADENO COR63 HINF PARA3 PNEU RSV Other BOPE FLUA HMPV PJP RHINO SAUR No attrib. Fig. 4.9: Pneumonia 'Aetiology Pies' for Children with WHO-defined Severe Pneu- monia by HIV-infection & -Exposure Status: Overall, Radiologically- confirmed Pneumonia & In-hospital Mortality ADENO = adenovirus; BOPE = B. pertussis ; COR63 = coronavirus NL63; FLUA = influenza A; HINF = non-type b H. influenzae ; HMPV = human metapneumovirus; No attrib. = no attribution; PARA3 = parainfluenza virus 3 (= parainfluenza virus 1); PJP = P. jirovecii ; RHINO = human rhinovirus; RSV = respiratory syncytial virus; SAUR = S. aureus. 'n' refers to the number of cases available in each analysis. All cases compared to controls Radiologically- confirmed pneumonia compared to controls 2.94.9 In-hospital death compared to controls 2721 n=296 28.2 2.94%.9% 4.9% 4.9 5n.8=17931 3n3=18 All children 27% 21%2 2% 3% 3 3% 28.2% 5.8% 5.8% 7.8% 5.8 31% 33% 16% 16 5%3 7%5 8% 8% 7 20.4 20.4% 8.7% 10.7% 7.8 8.7 16% 16 10% 10% 10 8810 3 110.7 45 7 10 16.8 2910%3% 5n=9930 1%4%5% n=6316.8%n=5 HEU 29% 16% 13% 5%5 5% 7% 7 12% 30% 20% 7%8 8% 11% 14 49.649.6% 33.6% 33.6 HIV- 16 13 29 29% 12 n=144 20 34 34% 14 26% 26 n=79 28 28% n=7 unexposed 51Q 2% 4% 2 5% 58% 14X 15% 155% 23% 4 6Q4 6 31.8 5 31.8% 5.4 5.4% 11.6% 11.6 n=39 14 44.7 2314.6 14.6% n=28n=6 HIV-infected 20.9% 20.9 14% 16.3% 16.3 44.7% 20.3% 20.3% 20.3 20.3 100% 100 ADENO CMV HBOV HMPV PARA3 RHINO SAUR No attrib. BOPE FLUA HINF PARA1 PJP RSV Other Fig. 4.10: Pneumonia 'Aetiology Pies'

for Children with WHO-defined **Very Severe Pneumonia** 989

by HIV-infection & -Exposure Status: Overall, Radiologically-confirmed Pneumonia & In-hospital Mortality ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR63 = coronavirus NL63; HINF = non-type b H. influenzae ; HMPV = human metapneumovirus; No attrib. = no attribution; PARA1 = parainfluenza virus 1; PARA3 = parainfluenza virus 3; PJP = P. jirovecii ; RHINO = human rhinovirus; RSV = respiratory syncytial virus; SAUR = S. aureus. 'n' refers to the number of cases avail- able in each analysis. 4.3Synopsis of

Chapter 4 Chapter 4 is the most important Chapter of 370

this thesis, and presents the results of the case- control analysis which permitted an estimation of the aetiologic profile of pneumonia in the PERCH South African cohort. The frequentist approach used in the case-control analysis has its limitations, chiefly in that at best it can only intimate associations with (and not firmly establish aetiology of) pneumonia case status, but also because – as it did not integrate the results of disparate elements of the PERCH case work-up (as did the Bayesian approach to pneumonia aetiology analysis used in the overarching PERCH paper) – a considerable proportion of children have an FA unassigned to any particular pathogen. Interrogation of the radiologically-confirmed cases, compared to controls, assisted in minimising the proportion of pneumonia cases that could not be attributed a pathogen associated with pneumonia. Key summary points from this Chapter are that: I. The prevalence of NP/OP carriage of three bacterial colonising organisms (non-type b H. influenzae , M. catarrhalis and S. pneumoniae) and CMV was high in the South African PERCH cohort, including when stratifying by HIV-infection and -exposure status; (a) After applying organism-specific cut-off density thresholds which best discriminated between cases and controls, prevalence of NP/OP carriage of the above-mentioned potential pneumonia pathogens decreased substantially; (b) The exercise in applying cut-off densities which best distinguished between cases and controls 'primed' the NP/OP and lytA whole blood data for the

logistic regression analyses which were used to estimate the 924

contribution of each potential pathogen to pneumonia aetiology in the South African PERCH cohort; II. Focussing on the sub-group of cases with radiologically-confirmed pneumonia assisted in limiting the FA of pneumonia attributed to 'unknown aetiology' in almost all analyses; III. In children with radiologically-confirmed pneumonia, the following 'top five' organisms ('top four' in HIV-infected children) detected on FTDResp-33 PCR testing of NP/OP swabs and/ or lytA PCR of whole blood were associated with case status, based on conditional logistic regression analyses which corrected for age (in months), season and all other pathogens: (a) All children: RSV (FA 0.28; 95% CI, 0.27 to 0.28), non-type b H. influenzae (FA 0.14; 95% CI, 0.10 to 0.17), S. aureus (FA 0.09; 95% CI, 0.06 to 0.10), P. jirovecii (FA 0.08; 95% CI, 0.07 to 0.08), adenovirus (FA 0.06;

95% CI, 0. 04 to 0. 06), parainfluenza virus 3 (FA 0. 06; 95% CI, 0. 05 to 0. 06) and human rhinovirus (FA 0. 06; 95% CI, 0. 04 to 0. 57

07); (b) HEU children: RSV (FA 0.31; 95% CI, 0.29 to 0.31), CMV (FA 0.16; 95% CI, 0.04 to 0.23), non-type b H. influenzae (FA 0.13; 95% CI, 0.11 to 0.14), S. aureus (FA 0.09;

95% CI, 0. 02 to 0. 12) and human rhinovirus (FA 0. 08; 95% CI, 0. 04 to 0. 09); (c) HIV- 14

unexposed children: RSV (FA 0.33; 95% CI, 0.31 to 0.33),

non type-b H. influenzae (FA 0.15; 95% CI, 0. 154

09 to 0.18), parainfluenza virus 3 (FA 0.07; 95% CI, 0.05 to 0.07), S. aureus (FA 0.06;

95% CI, 0. 03 to 0. 08), adenovirus (FA 0. 04; 95% CI, 0.02 to 0. 05) and HMPV (FA 0. 04; 95% CI, 0. 01 to 0. 59

06); (d) HIV-uninfected children, regardless of HIV-exposure status: RSV (aOR 0.31; 95% CI, 0.30 to 0.32), non-type b H. influenzae (aOR 0.13; 95% CI, 0.09 to 0.16), S. aureus

(aOR 0. 07; 95% CI, 0. 04 to 0. 09), adenovirus (aOR 0. 06; 95% CI, 0. 04 to 0. 06) and 62

parainfluenza virus type 3 (aOR 0.05;

95% CI, 0. 04 to 0. 05); (e) HIV-infected children: CMV (FA 0. 35; 95% CI, 0. 17 to 0. 29

42), P. jirovecii (FA 0.23; 95% CI, 0.21 to 0.23), RSV (FA 0.12; 95% CI, 0.10 to 0.12) and parainfluenza virus 3 (FA 0.10; 95% CI, 0.00 to 0.12); IV. Respiratory viruses were associated with case status in the majority

of children with radiologically-confirmed pneumonia 994

in HIV-uninfected children and HIV-infected children 318

on ART, whereas opportunistic pathogens predominated in ART-na¨ıve HIV-infected children; V. When stratifying the cohort by age group, the FA attributed to no identified organism was smaller in children <12 months, compared to children ≥12 months, and: (a) In children <12 months of age: i. RSV and

non-type-b H. influenzae contributed **the** largest portion **to the** 412

'aetiology pies' in all children, HEU children and HIV-unexposed children with radiologically-confirmed pneumonia; ii. CMV and P. jirovecii contributed the largest portion to the 'aetiology pie' in HIV- infected children with radiologically-confirmed pneumonia; iii. CMV and P. jirovecii were significantly associated with case status in HIV-infected and HEU children dying from pneumonia in-hospital; (b) In

children ≥12 months of age: i. **The** only group **of** children **in** 892

which S. pneumoniae (detected through lytA PCR of whole blood) was significantly associated with case status, was in HEU children with radiologically-confirmed pneumonia; ii. CMV detected on NP/OP swabs was the only organism associated with case status in HIV-infected children with radiologically-confirmed pneumonia; iii. Adenovirus and HMPV were the only two organisms that were demonstrated to be associated with in-hospital mortality. 5 Pneumonia and Aetiology-Specific Incidence Rates Chapter 5 presents pneumonia incidence rates for children requiring hospitalisation in Soweto during the time period in which PERCH was undertaken at the South African site. At the time of study conduct, CHBAH was the only public health facility in Soweto, and serviced the needs of >90% of the community that have no medical insurance cover when they require hospitalisation. Mid-estimate population denominators are used here (for reasons outlined in Section 2.4.4 and Appendices D and E). 5.1Pneumonia Incidence Rates

Stratified by HIV-infection and -Exposure Status Overall, **the** 136

incidence of pneumonia requiring hospitalisation for

WHO-defined severe or very severe pneumonia was 531

1 1755.0 (95% CI, 1 701.8 to 1 809.5) per 100 000 children under-5 (Table 5.1). Pneumonia incidence rates were consistently higher in younger age groups, compared to older children, as well as being

consistently higher in HIV-infected children compared to HIV-uninfected children 448

and, amongst

HIV-uninfected children, in HEU **compared to HIV-** unexposed **children (Table** 5.1). **The** 345

highest pneumonia incidence rate, 11 642.2 (95% CI, 9 419.2 to 14 231.9)

per 100 000 children, was observed **in HIV-** infected **children** in **the** 1

one- to 11-month age group, in the second year of the study (Table 5.1). The relative risks for pneumonia incidence were consistently

greater in HIV-infected compared to HIV-uninfected children with **the** 132

highest relative risk between the two groups being observed

in the 24 to 59 month age group in the 769

second year of the study (relative risk (RR) 6.73; 95% CI, 5.62 to 8.05) (Table 5.1). In the comparison

between HEU and HIV-unexposed children, 391

the relative risk for pneumonia hospitalisation

was also consistently higher in HEU children, particularly so in 391

the one- to 11-month age group

(RR 2. 00; 95% CI, 1. 81 to 2. 20) (Table 89

5.1). In sensitivity analysis which assumed that all

children with unknown HIV infection status were HIV-uninfected, the 867
relative risk for pneumonia

hospitalisation remained

consistently higher in HIV-infected compared to HIV-uninfected 448
children,

and HEU children

compared to HIV-unexposed children (data not 185

shown). 146 Tab. 5.1: Incidence of Pneumonia

(per 100 000 Population) in Soweto in Children 1 to 59 months of Age 226

– Mid Population Estimate Study Yeara Age Group

IR (95% CI) HIV+ IR (95% CI) HIV- 10

IR (95% CI) HEU IR (95% CI) HIV- unexposed IR (95% CI) All RR (95% CI) 10
(HIV+ vs. HIV-) RR (95% CI) (HEU vs. (months) HIV-

unexposed) Year 1 1 to 11 11 152.0 3 189.4 5 353.9 2 386.9 3 467.9 3.50 2.24 (8 978.9 to 13 692.1) (2 960.4 to 3 431.5) (4 788.4 to 5 967.8) (2 156.4 to 2 635.3) (3 233.1 to 3 715.4) (2.84 to 4.30) (1.94 to 2.59) Year 2 11 642.2 3 673.6 5 436.0 3 020.2 3 952.3 3.17 1.80 (9 419.2 to 14 231.9) (3 427.5 to 3 932.7) (4 866.1 to 6 054.4) (2 760.2 to 3 298.0) (3 701.3 to 4 215.9) (2.59 to 3.87) (1.57 to 2.06) Both Years 11 397.1 3 431.5 5 395.0 2 703.5 3 710.1 3.32 2.00 (9 818.0 to 13 157.9) (3 262.5 to 3 607.0) (4 990.3 to 5 823.8) (2 528.6 to 2 887.4) (3 537.4 to 3 889.1) (2.90 to 3.80) (1.81 to 2.20) Year 1 12 to 23 6 609.5 1 699.3 2 411.4 1 429.2 1 871.0 3.89 1.69 (4 965.3 to 8 624.0) (1 533.3 to 1 878.3) (2 037.4 to 2 834.3) (1 252.3 to 1 624.1) (1 699.6 to 2 054.9) (2.95 to 5.13) (1.38 to 2.07) Year 2 8 323.1 1 956.6 2 854.3 1 617.7 2 179.2 4.25 1.76 (6 463.2 to 10 551.6) (1 778.2 to 2 148.0) (2 446.0 to 3 311.4) (1 429.1 to 1 824.3) (1 994.0 to 2 377.0) (3.33 to 5.44) (1.46 to 2.13) Both Years 7 466.3 1 827.9 2 632.9 1 523.4 2 025.1 4.08 1.73 (6 200.3 to 8 914.8) (1 705.2 to 1 957.1) (2 352.7 to 2 937.2) (1 392.9 to 1 662.9) (1 898.1 to 2 158.4) (3.42 to 4.87) (1.51 to 1.98) Continued on next page . . . 147 Tab. 5.1, continued from previous page . . . Study Yeara Age Group

IR (95% CI) HIV+ IR (95% CI) HIV- 10

IR (95% CI) HEU IR (95% CI) HIV- unexposed IR (95% CI) All RR (95% CI) 10
(HIV+ vs. HIV-) RR (95% CI) (HEU vs. (months) HIV-

unexposed) Year 1 24 to 59 4 918.7 875.7 (806.7 to 949.0) 1 090.2 796.2 (719.5 to 878.8) 1 017.2 5.62 1.37 (4 081.4 to 5 877.2) (944.3 to 1 252.2) (944.0 to 1 094.5) (4.64 to 6.80) (1.16 to 1.62) Year 2 5 691.1 846.2 (778.4 to 918.3) 1 002.9 788.1 (711.8 to 870.3) 1 015.7 6.73 1.27 (4 787.4 to 6 715.7) (863.3 to 1 158.8) (942.6 to 1 093.1) (5.62 to 8.05) (1.07 to 1.52) Both Years 5 304.9 860.9 (812.3 to 911.8) 1 046.5 792.1 (737.7 to 849.6) 1 016.5 6.16 1.32 (4 680.8 to 5 989.0) (944.5 to 1 156.6) (964.4 to 1 070.6) (5.42 to 7.00) (1.17 to 1.49) Year 1 1 to 59 6 497.3 1 501.5 2 204.3 1 239.8 1 676.4 4.33 1.78 (5 739.9 to 7 326.9) (1 430.9 to 1 574.8) (2 040.9 to 2 377.3) (1 164.9 to 1 318.2) (1 603.0 to 1 752.3) (3.82 to 4.91) (1.61 to 1.96) Year 2 7 401.1 1 631.8 2 256.7 1 398.9 1 833.7 4.54 1.61 (6 591.1 to 8 283.1) (1 558.1 to 1 708.0) (2 091.3 to 2 431.7) (1 319.2 to 1 482.0) (1 756.9 to 1 913.0) (4.03 to 5.10) (1.47 to 1.77) Both Years 6 949.2 1 566.7 2 230.5 1 319.3 1 755.0 4.44 1.69 (6 389.9 to 7 544.4) (1 515.4 to 1 619.2) (2 113.6 to 2 352.2) (1 264.4 to 1 376.0) (1 701.8 to 1 809.5) (4.08 to 4.82) (1.58 to 1.81) a Time periods were from 17th August 2011 until 16th August 2012 (year 1 of the study), and from 17th August 2012 until 31st August 2013 (year 2 of the study); HEU = HIV-exposed, -uninfected;

HIV = human immunodeficiency virus type 1; **HIV+ = HIV-infected; HIV- = HIV-uninfected;** IR = **incidence** **61**

rate; RR = relative risk; Significant results are highlighted in bold font; Table produced using the stargazer package in R [66]. 148 5. Pneumonia and Aetiology-Specific Incidence Rates149 5.2Pathogen Specific Incidence Rates This Section presents pathogen-specific estimates of hospitalisation for severe and/ or very severe

pneumonia at the South African PERCH site, **25**

based on the FA for each organism derived in Chapter 4. The method by which pathogen-specific incidence rates were derived is described on page 80, and pathogen-specific incidence rates

are shown in Table 5.2. Adenovirus **The** relative **risk of** adenoviral pneumonia **was significantly higher in** HEU **children** **660**

under one year of age compared to HIV-unexposed

children (RR 1. 99; **95% CI, 1.** 49 **to 2.** **89**

67), with adenoviral pneumonia incidence rates of 352.4 (95% CI, 326.0 to 380.5) per 100 000 HEU children compared to 112.0 (95% CI, 104.8 to 119.6) per 100 000 HIV-unexposed children, respectively (Table 5.2). Bordetella pertussis Bordetella pertussis incidence rates were highest in children <12 months of age,

with an incidence rate of 90.2 **(95% CI,** 86.0 **to** **939**

94.5) per 100 000 children regardless of HIV-infection or -exposure status (Table 5.2). CMV CMV incidence rates were very high in

HIV-infected children, particularly so **in the** age group **<12 months of** **847**

age: incidence rate 4 989.9 (95% CI, 4 298.5 to 5 760.8) per 100 000 children. In

HIV-infected children ≥12 months of age, the **pneumonia** **554**

incidence rate associated with CMV declined to 1 468.8 (95% CI, 1 325.2 to 1 623.3) per 100 000 children (Table 5.2). Coronavirus NL63 As per the findings for other organisms, the incidence of coronavirus NL63 pneumonia hospital- isation was highest in children <12 months of age (235.5 (95% CI, 217.7 to 254.0) per 100 000 HEU children), tending to decrease with increasing age group (25.6 (95% CI, 24.5 to 26.8)

per 100 000 HIV-uninfected children from 12 **to** **5**

59 months of age) (Table 5.2). Tab. 5.2: Pathogen-specific Pneumonia Incidence

(per 100 000 Population) in Soweto – **Children 1** to 59 months **of Age** **226**

Organisma Age Groupb (months)

IR (95% CI) HIV+	IR (95% CI) HIV-	10

IR (95% CI) HEU	IR (95% CI) HIV- unexposed	IR (95% CI) All	RR (95% CI) (HIV+ vs. HIV-)	RR (95% CI) (HEU vs. HIV-	10

unexposed) ADENO 1 to 11 12 to 23 12 to 59 1 to 59 183.0 (174.0 to 192.4) 162.2 (151.3 to 173.7) 82.2 (78.7 to 85.9) 88.9 (86.0 to 91.8) 352.4 (326.0 to 380.5) 159.6 (151.2 to 168.3) 112.0 (104.8 to 119.6) 139.1 (127.2 to 151.8) 54.8 (52.5 to 57.1) 204.7 (195.1 to 214.5) 153.0 (143.4 to 163.1) 81.8 (78.6 to 85.2) 97.1 (94.2 to 100.1) 1.99 (1.49 to 2.67) 1.93 (1.59 to 2.34) BOPE 1 to 11 88.8 (84.4 to 93.3) 79.7 (74.5 to 85.1) 90.2 (86.0 to 94.5) 1 to 59 30.7 (29.7 to 31.7) 27.4 (26.2 to 28.6) 31.7 (30.8 to 32.7) CMV 1 to 11 4 989.9 (4 298.5 to 5 760.8) 12 to 59 1 468.6 114.2 (109.6 to 118.8) (1 325.2 to 1 623.3) 1 to 59 2 405.0 363.0 (344.0 to 382.8) (2 211.4 to 2 610.9) COR63 1 to 11 235.3 (217.7 to 254.0) 12 to 23 64.3 (59.9 to 68.8) 84.8 (77.6 to 92.6) 12 to 59 25.6 (24.5 to 26.8) 39.4 (37.3 to 41.6) 1 to 59 71.0 (67.3 to 74.9) Continued on next page . . . 150 Tab. 5.2, continued from previous page . . . Organisma Age Groupb

IR (95% CI) HIV+	IR (95% CI) HIV-	10

IR (95% CI) HEU	IR (95% CI) HIV- unexposed	IR (95% CI) All	RR (95% CI) (HIV+ vs. HIV-)	RR (95% CI) (HEU vs. (months)	HIV-	10

unexposed) FLUA 12 to 23 12 to 59 149.4 (139.4 to 159.9) 81.5 (78.0 to 85.2) 170.6 (158.3 to 183.7) 45.2 (42.7 to 47.7) 134.5 (126.0 to 143.3) 82.8 (79.5 to 86.2) 2.16 (1.78 to 2.62) 1 to 59 49.9 (48.3 to 51.6) 97.5 (92.4 to 102.8) 31.1 (29.8 to 32.5) 48.5 (47.0 to 50.0) 1.98 (1.55 to 2.53) FLUB 1 to 59 21.1 (20.4 to 21.8) 23.2 (22.2 to 24.2) 18.9 (18.4 to 19.5) HBOV 1 to 11 1 to 59 102.6 (97.6 to 107.9) 40.8 (39.5 to 42.2) 325.8 (301.4 to 351.7) 26.6 (25.5 to 27.7) 119.5 (114.0 to 125.3) 60.5 (58.6 to 62.4) HIB 1 to 59 16.9 (16.3 to 17.4) 19.0 (18.4 to 19.5) HINF 1 to 11 12 to 23 3 210.3 (2 765.5 to 3 706.3) 516.6 (491.1 to 543.0) 306.0 (285.4 to 327.6) 623.5 (576.7 to 673.1) 505.7 (473.0 to 540.1) 609.7 (581.4 to 639.2) 5.37 (3.77 to 7.66) 1.16 (0.89 to 1.51) 1 to 59 204.7 (198.0 to 211.6) 300.4 (284.6 to 316.8) 193.6 (185.6 to 201.9) 247.4 (239.9 to 255.1) 1.36 (1.15 to 1.60) HMPV1 to 11164.2 (156.1 to 172.6)124.8 (116.7 to 133.3)154.6 (147.4 to 162.0) 24 to 59121.7 (114.8 to 128.9)117.9 (111.9 to 124.2) 12 to 5961.2 (58.6 to 64.0)63.9 (61.3 to 66.5) 1 to 5975.4 (72.9 to 77.9)56.2 (53.8 to 58.6)75.8 (73.5 to 78.1) MCAT 12 to 5956.9 (53.8 to 60.0) Continued on next page . . . 151 Organisma Age Groupb

IR (95% CI) HIV+	IR (95% CI) HIV-	10

IR (95% CI) HEU	IR (95% CI) HIV- unexposed	IR (95% CI) All	RR (95% CI) (HIV+ vs. HIV-)	RR (95% CI) (HEU vs. (months)	HIV-	10

unexposed) PARA1 1 to 11 40.8 (38.8 to 42.9) 59.9 (56.0 to 63.9) 48.3 (46.1 to 50.6) 12 to 23 88.2 (82.3 to 94.4) 83.3 (76.2 to 91.0) 80.6 (75.6 to 86.0) 24 to 59 51.6 (48.9 to 54.3) 12 to 59 50.1 (48.0 to 52.4) 54.3 (51.4 to 57.3) 53.9 (51.8 to 56.1) 1 to 59 31.4 (30.4 to 32.5) 41.4 (39.7 to 43.2) 36.0 (34.9 to 37.1) PARA3 1 to 11 195.1 (185.5 to 205.1) 200.1 (187.2 to 213.7) 258.5 (246.5 to 271.0) 12 to 23 84.4 (78.7 to 90.3) 115.6 (105.7 to 126.2) 74.7 (70.0 to 79.6) 12 to 59 1 to 59 671.8 (617.7 to 729.3) 75.7 (73.3 to 78.3) 51.9 (49.1 to 54.9) 89.6 (85.9 to 93.4) 100.8 (97.7 to 103.9) 7.12 (5.16 to 9.8) PJP 1 to 11 3 635.7 200.6 (190.7 to 210.8) 381.1 (352.5 to 411.4) 113.6 (106.2 to 121.3) 369.7 (352.4 to 387.5) 11.83 2.03 (3 132.0 to 4 197.4) (8.89 to 15.74) (1.54 to 2.67) 1 to 59 1 601.6 68.8 (66.5 to 71.1) 125.7 (119.1 to 132.5) 40.2 (38.5 to 41.9) 132.8 (128.8 to 136.9) 13.29 1.98 (1 472.7 to 1 738.8) (11.10 to 15.92) (1.59 to 2.46) PNEU 24 to 59 87.2 (82.3 to 92.3) 133.6 (126.8 to 140.7) 12 to 59 212.1 (196.7 to 228.3) 1 to 59 58.4 (56.6 to 60.2) Tab. 5.2, continued from previous page . . . 3 Continued on next page . . . 152 Tab. 5.2, continued from previous page . . . Organisma Age Groupb

IR (95% CI) HIV+	IR (95% CI) HIV-	10

IR (95% CI) HEU	IR (95% CI) HIV- unexposed	IR (95% CI) All	RR (95% CI) (HIV+ vs. HIV-)	RR (95% CI) (HEU vs. (months)	HIV-	10

unexposed) RHINO 1 to 11 173.7 (165.2 to 182.6) 199.4 (190.1 to 209.0) 12 to 23 140.3 (130.9 to 150.2) 192.0 (180.0 to 204.6) 12 to 59 64.7 (61.9 to 67.6) 206.8 (191.8 to 222.6) 84.9 (81.6 to 88.4) 1 to 59 80.7

(78.1 to 83.4) 173.0 (164.0 to 182.5) 98.5 (95.5 to 101.6) RSV 1 to 11 1 640.3 1 296.2 1 959.3 1 074.3 1 261.3 1.22 1.50 (1 413.0 to 1 893.7) (1 232.4 to 1 362.5) (1 812.3 to 2 115.0) (1 004.7 to 1 147.3) (1 202.6 to 1 322.2) (0.71 to 2.09) (1.30 to 1.73) 12 to 23 269.8 (251.7 to 288.8) 260.6 (238.3 to 284.5) 274.9 (257.7 to 293.0) 12 to 59 133.6 (127.8 to 139.5) 125.7 (116.6 to 135.4) 133.1 (125.9 to 140.5) 131.7 (126.4 to 137.1) 0.96 (0.71 to 1.30) 1 to 59 836.2 (768.9 to 907.8) 490.4 (474.4 to 506.9) 685.4 (649.5 to 722.8) 428.8 (410.9 to 447.2) 490.0 (475.1 to 505.2) 1.66 1.38 (1.19 to 2.30) (1.24 to 1.53) SAUR 1 to 11 237.0 (225.3 to 249.1) 286.5 (273.2 to 300.3) 24 to 59 124.0 (117.0 to 131.3) 127.1 (120.6 to 133.8) 12 to 59 66.8 (63.9 to 69.8) 55.9 (52.9 to 59.0) 102.4 (98.3 to 106.6) 1 to 59114.1 (110.4 to 117.9)195.7 (185.4 to 206.4)82.8 (79.4 to 86.4)149.5 (144.9 to 154.1)1.73 (1.44 to 2.09) a Incidence rates were derived by obtaining the product of each group's incidence rate (see Table 5.1) and the FA for each pathogen (as derived in the case-control conditional logistic regression analyses presented in Chapter 4); b Only age groups with available data are listed in this Table. ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR63 = coronavirus NL63;

FLUA = influenza A; FLUB = influenza B; HBOV = human bocavirus; HEU = **HIV-** **341**

exposed, -uninfected;

Hib = H. influenzae type b; HINF = non **-type** b **H. influenzae** **36**

;

HIV = human immunodeficiency virus type 1; **HIV+ = HIV-infected; HIV- = HIV-uninfected;** **61**

HMPV = human metapneumovirus; IR = incidence rate; MCAT = M. catarrhalis ; PARA1 = parainfluenza virus 1; PARA3 = parainfluenza virus 3; PJP = P. jirovecii ; RHINO = human rhinovirus; RR = relative risk; RSV = respiratory syncytial virus; SAUR = S. aureus ; Significant results are highlighted in bold font; Table produced using the stargazer package in R [66]. 153 Influenza Viruses Influenza A was encountered with significantly higher frequency in HEU compared to HIV- unexposed children from one to 59

months of age (RR 1. 98; **95% CI, 1.** **178**

55 to 2.53) and the highest influenza A incidence rates were observed

in the 12 to 59 month age group **385**

of HEU children (170.6 (95% CI, 158

.3 to 183 **.7) per 100 000 HIV-uninfected children).** **5**

Influenza B-associated pneumonia hospitalisation rates were considerably lower than those of influenza A (21.1 (95% CI, 20.4 to 21

.8) per 100 000 HIV-uninfected **children <5 years of age in** **148**

HIV-uninfected children) (Table 5.2). Human bocavirus The highest incidence rates of hospitalisation associated with human bocavirus occurred

in children<12 **months of age,** especially **in** HEU **children in** whom **the** **530**

incidence rate was 325.8 (95% CI, 301.4 to 351.7) per 100 000 children (Table 5.2). Haemophilus influenzae The incidence of pneumonia hospitalisation associated with H. influenzae type b was low overall (19.0 (95% CI, 18.4 to 19.5) per 100 000 children). In contrast to disease associated with H. influenzae type b, pneumonia hospitalisation rates attributable to non-type b H. influenzae were very high, particularly

in children<12 **months of age, and** HIV-infected **children. The** **530**

relative risk for pneumonia hospitalisation associated with non-type b H. influenzae was 5.37 (95% CI, 3.77 to 7.66) in the comparison between

HIV-infected and -uninfected children<12 months of age 975

(incidence rates 3 210.3 (95% CI, 2 765.5 to 3 706.3) per 100 000 children and 516.6 (95% CI, 491.1 to 543.0) per 100 000 children, respectively). Overall, HEU children <59 months of age had a higher risk of pneumonia hospitalisation associated with H. influenzae than did HIV-unexposed children

(RR 1. 36; 95% CI, 1. 15 to 1. 60) (Table 870

5.2). HMPV HMPV-associated pneumonia incidence requiring hospitalisation

was highest in the age group<12 months of age, and 956

declined with increasing age. In HIV-uninfected children <12%

months of age, the incidence rate (per 100 000 583

children between the ages of 1 and 11 months) was 859

164.2 (95% CI, 1561. to 172.6) (Table 5.2). Moraxella catarrhalis The incidence of pneumonia hospitalisation associated with M. catarrhalis was 56.9 (95% CI, 53.8 to 60.0) per 100 000 children amongst the HIV-unexposed

children between the ages of 12 and 59 months 259

(Table 5.2). Parainfluenza viruses The highest incidence rate of hospitalisation associated with parainfluenza virus type 1 was in the 12 to 23 month age group (88.2 (95% CI, 82.3 to 94.4) per 100 000 HIV-uninfected children) which contrasted sharply against the pattern of pneumonia incidence associated with

parainfluenza virus type 3, in which the 470

highest incidence rates for hospitalisation were observed in children <12 months of age (195.1 (95% CI, 185.5 to 205.1) per 100 000

HIV-uninfected children). Overall, HIV-infected children had a 7. 875

12-fold (95% CI, 5.16 to 9.83) greater relative risk of hospitalisation associated with parainfluenza virus type 3 compared to HIV-uninfected children (Table 5.2). Pneumocystis jirovecii The highest incidence rates of pneumonia hospitalisation associated with P. jirovecii occurred in children <12 months of age, being exceptionally high (3 635.7 (95% CI, 3 312.0 to 4 197.4)

per 100 000 children) in HIV- infected children. The 1

relative risk for P. jirovecii associated pneumonia hospitalisation was 11.83-fold greater (95% CI, 8.89 to 15.74) in

HIV-infected infants compared to those that were HIV-uninfected. Similarly, HEU infants 1

had a 2.03-fold greater (95% CI, 1.54 to 2.76) relative risk for hospitalisation associated with P. jirovecii than did HIV-unexposed children (Table 5.2). Pneumococcus Pneumonia hospitalisation associated with S. pneumoniae was only observed in children >12 months of age using the FA approach in the case-control analysis of the PERCH data. The highest pneumococcal-associated pneumonia incidence rate

(in the 12 to 59 month age group) 385

was observed in HEU children: 212.1 (95% CI, 196.7 to 228.3) per 100 000 children (Table 5.2). Human rhinovirus Human rhinovirus-associated pneumonia hospitalisation incidence rates could be derived for HIV-

uninfected children and the cohort as a whole, but were highest (206.8 (95% CI, 191.8 to 222.6) per 100 000 children) in HEU

children between the ages of 12 and 59 months of 259

age (Table 5.2). RSV Pneumonia hospitalisation rates attributable to RSV were uniformly very high (>1 000 per 100 000 children) in children

<12 months of age, regardless of HIV-infection of -exposure status. In HIV-infected children 97

1 640.3 (95% CI, 1 413.0 to 1 893.7) per 100 000

children between the ages of one and 11 months were 129

hospitalised with RSV-associated pneumonia, compared to 1 296.2 (95% CI, 1 232.4 to 1 362.5)

per 100 000 HIV-uninfected children. The relative risk for RSV- 143

associated pneumonia hospitalisation was significantly

greater in HIV-infected compared to HIV-uninfected children 132

overall (RR 1.66; 95% CI, 1.19 to 2.30). HEU children – particularly those <12

months of age – had a significantly greater relative risk of 917

RSV-associated pneumonia hospitalisation

compared to HIV- unexposed children (RR 1.50; 95% CI, 1. 447

30 to 1.73) (Table 5.2). Staphylococcus aureus The incidence of S. aureus associated pneumonia hospitalisation was high in the HIV-uninfected group <12 months of age (237.0 (95% CI, 225.3 to 249.1) per 100 000 children). Overall, HEU children had a significantly greater relative risk of pneumonia hospitalisation associated with S. aureus than did HIV-unexposed

children (RR 1.73; 95% CI, 1. 44 to 2. 89

09) (Table 5.2). 5.3Synopsis of Chapter 5 This Chapter presents estimates of pneumonia hospitalisation incidence rates, stratified by HIV-infection and -exposure status, age group and pathogen, for

children under-5 years of age resident in Soweto during PERCH study 15

conduct. An important aspect of these analyses, is the estimation of relative risk for hospitalisation attributable to each pathogen according to HIV-infection and -exposure status. Pertinent findings from these analyses can by summarised as follows: I. Regardless of HIV-infection or -exposure status, the incidence rate for pneumonia hospitalisa- tion declined with advancing age group; II. Pneumonia hospitalisation incidence rates were exceptionally high

in HIV-infected children compared to HIV-uninfected children, 35

with consistently higher

relative risk for pneumonia hospitalisation in HIV-infected children compared to HIV-uninfected 716

children regardless of age group; III. Pneumonia hospitalisation incidence rates amongst HEU children were consistently higher than that of HIV-unexposed children, regardless of age group; IV. Incidence rates for

pneumonia hospitalisation, stratified by pathogen, tended to decrease with advancing age group, regardless of HIV-infection of -exposure status. Exceptions to this rule included adenovirus in HIV-unexposed children and parainfluenza virus type 1, in which higher incidence rates of pneumonia hospitalisation were observed

in the 12 to 23 month age group compared to the<12 month age group;	507

V. In the comparison

between HIV-infected and -uninfected children, the following	241

pathogens were associated with a significantly greater

burden of pneumonia hospitalisation in HIV-infected children: (a)	823

Non-type b H. influenzae

in children <12 months of age (RR 5.37; 95% CI,	844

3.77 to 7.66); (b) Parainfluenza virus type 3 in children <60

months of age (RR 7.12; 95% CI, 5.16 to 9 .83);	59

(c) Pneumocystis jirovecii in children one to 11 months of age (RR 11.83; 95% CI, 8.89 to 15.74) and <60 months of age (RR 13.29; 95% CI, 11.10 to 15.92); (d) RSV in children <60

months of age (RR 1. 66; 95% CI, 1.	178

19 to 2.30); VI. In the comparison between HEU and HIV-unexposed children, the following pathogens

were associated with a significantly greater burden of pneumonia hospitalisation in HEU children:	319

(a) Adenovirus, particularly

in children one to 11 months of age	319
(RR 1. 99; 95% CI, 1. 49 to 2. 67), and overall (RR 1 .93; 95% CI, 1.59 to	89

2.34); (b) Influenza A, particularly in the 12 to 59 month age

group (RR 2. 16; 95% CI, 1. 78 to 2.	428

62); (c) Non-type b H. influenzae in children <60

months of age (RR 1. 36; 95% CI, 1.	178

15 to 1.60); (d) Pneumocystis jirovecii, particularly in children one to 11

months of age (RR 2. 03; 95% CI, 1. 54 to	555

2.67); (e) RSV, particularly in children one to 11

months of age (RR 1. 50; 95% CI, 1.	178

30 to 1.73); (f) Staphylococcus aureus in children <60

months of age (RR 1. 73; 95% CI, 1. 178

44 to 2.09). 6 Tuberculosis in the South African PERCH Cohort This Chapter presents work which was done in

order to describe the burden of tuberculosis in the South African PERCH cohort, the 798

clinical presentation of tuberculosis cases and factors associated with a clinical decision to investigate children hospitalised

with WHO-defined severe or very severe pneumonia for 18

PTB. Most of this work has been published [484]. The main thrust of the published work was to evaluate to what extent an additional IS specimen enhanced the yield of culture-confirmed Mtb. A further component of the tuberculosis-related work presented here was to evaluate the potential role of Mtb

as a risk factor for acute CAP in children. A subset of 54

PERCH controls were screened by means of Mantoux testing, so as to evaluate the prevalence of asymptomatic Mtb infection in the control group, and these were compared to cases that had available Mantoux results. Cases that had microbiologically-confirmed PTB were included in the group of 'TB infected' cases by virtue of the fact that they presented with clinical features of PTB and had Mtb cultured on clinical specimens. 6.1Case Investigation for Mtb Tuberculosis was investigated for in 906 (98.5%) of the 920 South African PERCH cases by submission of IS and/ or GAs for Mtb culture (Figure 6.1). Gastric aspirates were requested at the discretion of attending clinicians. 6.1.1 Features Associated with Completeness of IS Collection in PERCH: South African Site Most (785/906; 86.6%) of the PERCH cases that were investigated for PTB had two IS specimens submitted for Mtb culture, however a subset had only one specimen submitted (Figure 6.1). After adjusting for age (in months) at PERCH enrolment, the only factor negatively associated with submission of two IS specimens was

in-hospital mortality (aOR 0. 04; 95% CI, 0. 02 to 0. 774

12) (see Table H.1 in Appendix H). Lethargy

(aOR 0. 34; 95% CI, 0. 12 to 0. 99) and in-hospital mortality (aOR 0. 05; 95% CI, 0. 02 to 0. 62

12) were associated with submission of one rather than two ISs on multivariate analysis (Table H.1). 159 920 children with severe or very severe

pneumonia at the South African PERCH site 906 with at least one specimen collected 2

for Mtb culture 55 with one IS 785 with two ISs 66 with no IS 4 without IS results 9 without any IS result 28 with 2nd IS result only 51 with IS result + 29 with 1st + IS result only 719 with both IS results: Yield Analysis 1 =799 with 1st IS result Did not contribute to yield analysis 22 with 1st GA result 15 with 1st and 2nd GA results 8 with 1st , 2nd and 3rd GA results 15 with 1st ++ GA result 13 with 1st and ++ 2nd GA results 8 with 1st , 2nd ++ and 3rd GA results 390 with 1st GA result: Yield Analysis 5 300 with 1st and 2nd GA results: Yield Analysis 6 185 with 1st , 2nd and 3rd GA results: Yield Analysis 7 427 with 1st IS =and 1st GA result: Yield Analysis 2 328 with 1st IS =and 2 GA results: Yield Analysis 3 201 with 1st IS result =and 3 GA results: Yield Analysis 4 6. Tuberculosis in the South African PERCH Cohort 160 Fig. 6.1: Specimens Available for IS and GA Diagnostic Yield Analysis GA = gastric aspirate; IS = induced sputum; Mtb = M. tuberculosis. 6.1.2Features Associated with Ward Clinician Decision to Collect GAs After adjusting for age (in months) at PERCH enrolment, factors significantly associated with clinician decision to submit GA specimens for investigation of tuberculosis included a clinical

history of fever (aOR 1. 61; 95% CI, 1. 889

23 to 2.12), HIV infection (aOR 2.08; 95% CI, 1.36 to 3.17) and a positive Mantoux response (aOR 2.78; 95% CI, 1.33 to 5.85) (Table H.2, Appendix H). Very severe pneumonia (aOR 0.62; 95% CI, 0.47 to 0.82),

the pneumonia danger signs of lethargy (aOR 0.39; 95% CI, 0.22 to 0.71) and inability to feed or vomiting everything (aOR 0.30; 95% CI, 0.15 to 0.59), the clinical finding of stridor

(aOR 0. 35; 95% CI, 0. 19 to 0. 66), and in-hospital death (aOR 0. 37; 95% CI, 0. 18 to 0. 62

75) were associated with clinician decision not to submit GA (Table H.2). In multivariate analysis, only positive Mantoux (aOR 3.13; 95% CI, 1.30 to 7.54), HIV-infection (aOR 2.62;

95% CI, 1. 11 to 6. 17) and older age (aOR 959

1.02; 95% CI, 1.00 to 1.05) were significantly associated with 305

a clinician decision to submit GAs for investigation of

tuberculosis in children <5 years of age 25

at the South African PERCH site (Table H .2). 25

In multivariate analysis, lethargy

(aOR 0. 23; 95% CI, 0. 07 to 0. 74), stridor (aOR 0. 19; 95% CI, 0. 06 to 0. 58) and 62

empiric anti-tuberculosis therapy initiated on the day of hospitalisation (aOR 0.05;

95% CI, 0. 0 to 0. 62) were negatively associated with 57

clinician decision to submit GAs on children under their care (Table H.2). 6.1.3Clinically and Microbiologically-confirmed PTB in the South African PERCH Cohort A clinical or microbiologically-confirmed diagnosis of tuberculosis was made in 146 (15.9%) of the 920 PERCH cases, 27 (18.4%) of which were culture-confirmed. In

multivariate analysis, factors significantly associated with a diagnosis of (clinically or 957

microbiologically-confirmed) tuberculosis included a positive Mantoux response (aOR 26.48; 95% CI, 12.72 to 55.14), WAZ ≤-3 (aOR 4.16; 95% CI, 2.12 to 8.20), WAZ >-3 to <-2 (aOR 3.01; 95% CI, 1.55 to 5.83) and increasing age (aOR 1.03;

95% CI, 1.01 to 1. 05) (Table H. 887

3, Appendix H). Clinical characteristics

of the 27 culture-confirmed tuberculosis cases are shown in 2

Appendix H (Table H.4). Tuberculosis in HIV-uninfected children Mycobacterium tuberculosis was cultured in 13 (1.8%) of the 740 HIV-uninfected children that had IS submitted for Mtb culture (Table 6.1). Furthermore, Mtb was cultured in 14 (3.3%) of the 418 HIV-uninfected children in whom GA were submitted. Sixty-five HIV-uninfected children were ventilated, and therefore underwent ETT sampling in order to establish a diagnosis of PTB, and one (1.5%) of these 65 children – HEU with radiologically-confirmed pneumonia – had an ETT specimen that was culture-positive for Mtb (Table 6.1). Fifty-one (14.9%) of the 342 HIV-uninfected children that had a recorded Mantoux response, had Mantoux induration that was positive. The highest Mantoux positivity rate (20/124, 16.1%) was seen in HEU children (Table 6.1). Tuberculosis in HIV-infected children None of the 100 IS specimens submitted for Mtb culture from

HIV-infected children with WHO- defined severe or very severe pneumonia, 16

(Table 6.2). Gastric aspirates were collected in 80 (69.6%) of the HIV-infected children, and two (2.5%) were positive for Mtb on culture (Table 6.2). The positivity yield for Mtb culture was highest in HIV-infected children in whom ETT specimens had been collected on mechanically ventilated children (n=7), in one (14.3%) was culture positive for Mtb (Table 6.2). Of 52 HIV-infected children with available Mantoux test results, seven (13.5%) were positive (Table 6.2). 6.2The Diagnostic Utility of IS and GA in Establishing a Microbiologic Diagnosis of Tuberculosis Figure 6.1 summarises the numbers of IS and GA specimens submitted from South African PERCH cases. Of 2 782 specimens submitted for investigation of PTB, 157 (5.6%) were not processed for Mtb culture. A first IS Mtb culture result was available from 799 children, of which 328 (41.1%) had results available for the first IS specimen and ≥2 GAs and 300 (37.5%) had results available for two ISs and ≥2 GAs (Figure 6.1). Tab. 6.1: Tuberculosis Work-up Results for HIV-uninfected Cases Category All cases (n=805) (%) CXR+ Cases (n=435) (%) Died in Hospital (n=20) (%) HEU (n=298) (%) HIV-unexposed (n=465) (%) Unknown Exposure (n=42) (%) Number of children with IS 740/805 (91.9) 387/435 (89.0) 8/20 (40.0) 269/298 (90.3) 433/465 (93.1) 37/42 (88.1) specimens IS Mtb Culture Pos 13/740 (1.8) 9/387 (2.3) 0/8 (0.0) 8/269 (3.0) 5/433 (1.2) 0/37 (0.0) Number of children with GA 418/805 (51.9) 238/435 (54.7) 5/20 (25.0) 154/298 (51.7) 243/465 (52.3) 21/42 (50.0) specimens 1 specimen 84 45 1 28 49 7 2 specimens 117 66 2 40 73 4 3 specimens 208 122 2 82 116 10 4 specimens 7 4 0 3 4 0 5 specimens 2 2 0 1 1 0 GA Mtb Culture Pos 14/418 (3.3) 10/239 (4.2) 0/5 (0.0) 6/154 (3.9) 8/243 (3.3) 0/21 (0.0) Continued on next page . . . 163 Tab. 6.1, continued from previous page . . . Category All cases (n=805) (%) CXR+ Cases (n=435) (%) Died in Hospital (n=20) (%) HEU (n=298) (%) HIV-unexposed (n=465) (%) Unknown Exposure (n=42) (%) Number of children with ETT 65/805 (8.1) 51/435 (11.7) 10/20 (50.0) 30/298 (10.1) 32/465 (6.9) 3/42 (7.1) specimens 1 specimen 17 11 3 9 8 0 2 specimens 47 39 7 21 24 2 3 specimens 1 1 0 0 0 1 ETT Mtb Culture Pos 1/65 (1.5) 1/51 (2.0) 0/10 (0.0) 1/30 (3.3) 0/32 (0.0) 0/3 (0.0) Available Mantoux results 342/805 (42.5) 185/435 (42.5) 2/20 (10.0) 124/298 (41.6) 198/465 (42.6) 20/42 (47.6) Neg 291/342 (85.1) 164/185 (88.6) 2/2 (100.0) 104/124 (83.9) 168/198 (84.8) 19/20 (95.0) Pos 51/342 (14.9) 21/185 (11.4) 0/2 (0.0) 20/124 (16.1) 30/198 (15.2) 1/20 (5.0) CXR+ = radiologically-confirmed pneumonia;

PCR = polymerase chain reaction; Pos = positive; Table produced using the stargazer package in R [66]. 164 Tab. 6.2: Tuberculosis Work-up Results for HIV-infected Cases Category All cases (n=115) (%) CXR+ Cases (n=89) (%) Died in Hospital (n=17) (%) Number of children with IS 100/115 (87.0) 80/89 (89.9) 11/17 (64.7) specimens IS Mtb Culture Pos 0/100 (0.0) 0/80 (0.0) 0/11 (0.0) Number of children with GA 80/115 (69.6) 64/89 (71.9) 7/17 (41.2) specimens 1 specimen 15 13 1 2 specimens 22 17 4 3 specimens 37 28 1 4 specimens 4 4 1 5 specimens 2 2 0 6. Tuberculosis in the South African PERCH Cohort 165GA Mtb Culture Pos 2/80 (2.5) 2/64 (3.1) 0/7 (0.0) Continued on next page . . . Tab. 6.2, continued from previous page . . . Category All cases (n=115) (%) CXR+ Cases (n=89) (%) Died in Hospital (n=17) (%) Number of children with ETT specimens 7/115 (6.1) 6/89 (6.7) 1/17 (5.9) ETT Mtb Culture 1 specimen220 2 specimens541 Pos 1/7 (14.3) 1/6 (16.7) 0/1 (0.0) 6. Tuberculosis in the South African PERCH Cohort 166 Available Mantoux results 52/115 (45.2) 43/89 (48.3) 2/17 (11.8) Neg 45/52 (86.5) 38/43 (88.4) 2/2 (100.0) Pos 7/52 (13.5) 5/43 (11.6) 0/2 (0.0) CXR+ = radiologically-confirmed pneumonia;

PCR = polymerase chain reaction; Pos = positive; Table produced using the stargazer package in R [66]. Yield analysis 1: 1st versus 2nd IS specimen Twelve specimens were available in the head-to-head comparison between the first and second IS specimen, amongst 719 cases that had two IS specimens submitted. Culture positivity when interrogating two IS specimens was 1.7%. Six (50.0%) of the culture-confirmed Mtb cases were detected through the first IS specimen alone and an additional four cases (33.3% of the 12 culture-confirmed cases in this comparison) were detected through submission of the second IS specimen only. Eight culture-confirmed Mtb cases were detected through the first and second IS specimens (Figure 6.2). Yield analysis 2: 1st IS versus 1st GA specimen Four hundred, twenty-seven children had results available for the first IS and first GA specimens, and of these 11 (2.6%) were culture-positive for Mtb. The first GA contributed a substantial additional yield to the diagnosis of culture-confirmed Mtb in this analysis (6 (54.5%) of the 11 culture-confirmed cases), although not statistically better than the yield from the first IS (Figure 6.2). Yield analysis 3: 1st IS versus the first two GA specimens Twelve (3.7%) of 328 children that had available results for the first IS and first two GA specimens were culture-positive for Mtb. Similarly to the findings of Analysis 2 (above), the two GAs contributed a substantial (66.7%) but not statistically significant additional yield over the first IS (Figure 6.2). Yield analysis 4: 1st IS versus first three GA specimens Six (3.0%) of the 201 children with available culture results for the first IS and first three GA

specimens were culture-positive for Mtb and GAs contributed an 83.3% additional yield to IS in this analysis (albeit not statistically significant) (Figure 6.2). 6. Tuberculosis in the South African PERCH Cohort 168 Comparison Culture-confirmed PTB Added Yield (%) P-value Number of Positive Specimens # Group 1 Group 2 N n % Group 1 Group 2 · · · 1 2 3 4 5 6 7 8 9 10 11 12 1 IS1 IS2 719 12 1.7 50.0 33.3 0.752 2 IS1 GA1 427 11 2.6 27.3 54.5 0.505 3 IS1 GA1,2 328 12 3.7 16.7 66.7 0.114 4 IS1 GA1,2,3 201 6 3.0 16.7 83.3 0.221 5 IS1,2 GA1 390 11 2.8 27.3 45.5 0.723 6 IS1,2 GA1,2 300 12 4.0 16.7 58.3 0.182 7 IS1,2 GA1,2,3 185 6 3.2 16.7 66.7 0.371 Fig. 6.2: Additional Yield of Group 2 to Group 1 Specimens Submitted for Mtb Culture GA = gastric aspirate; GA1 = 1st gastric aspirate; GA1,2 = 1st and 2nd gastric aspirates; GA1,2,3 = 1st , 2nd and 3rd gastric aspirates; IS = induced sputum; IS1 = 1st induced sputum; IS1,2 = 1st and 2nd induced sputum specimens; Mtb = M. tuberculosis ; n = numerator (the number of Mtb culture-positive cases detected in each analysis); N = denominator (the number of cases with available results from the specimens being compared in each analysis); P-values were derived using the McNemar $\chi 2$ test. Group 1 specimens are highlighted in light red, Group 2 specimens in light blue, and Mtb cultures positive on both Group 1 and Group 2 specimens are highlighted in purple . Yield analysis 5: two IS specimens versus the 1st GA specimen Of the 390 children with available results for two IS specimens and the first GA, 11 (2.8%) were culture-positive for Mtb. The first GA contributed an additional 45.5% yield of Mtb in this comparison (Figure 6.2). Yield Analysis 6: two IS specimens versus the first two GA specimens The greatest test positivity for Mtb culture was observed in children that had two IS and two GA specimens submitted for investigation of PTB: 12 (4.0%) of 300 children were positive for Mtb in this analysis. In head-to-head comparison, two GAs contributed a substantial (although not statistically significant) additional yield of culture-confirmed Mtb over IS specimens (58.3% versus 16.7%) (Figure 6.2). Yield analysis 7: two IS specimens versus first three GA specimens A considerably smaller cohort of children (n=185) had available results for the analysis of culture yield from a full complement of tests (two ISs and three GAs), and of these, six (3.2%) were positive for Mtb. The added yield of three GAs to the diagnosis of culture-confirmed PTB was 66.7% (compared to only 16.7% for a full complement of IS specimens). Once again, small numbers limited the statistical power to discern statistical significance in this analysis (Figure 6.2). 6.3Mantoux Responses in Cases Compared to Controls As highlighted in Tables 6.1 and 6.2, 394 (42.8%) of the 920 South African PERCH cases had available Mantoux response results, and of these 58 (14.7%) were positive according to WHO criteria [480]. A further subset of cases had Mantoux responses measured at the 30-day follow-up appointment, after recovery from their acute illness, and of these 14 (36.8%) of 38 were Mantoux positive. The mean time period between enrolment into PERCH and outpatient review of the Mantoux reaction was 10.0 weeks (SD, 6.1 weeks). Fifteen (39.5%) of the 38 cases had Mantoux responses recorded during their PERCH hospitalisation episode, and at the 30-day follow-up assessment and of these, two (13.3%) had converted from negative to a positive Mantoux response, three (20.0%) had reverted from being Mantoux positive during the hospitalisation to Mantoux negative at follow-up, and the remaining 10 (66.7%) children had Mantoux results that were concordant at both time points (five Mantoux positive and five Mantoux negative at both assessments). In the small sub-study of control Mantoux screening, 10 (17.9%) of 56 controls were noted to have positive Mantoux responses and were thus considered to have evidence of infection with Mtb. The median time between inoculation of PPD and reading of the Mantoux response in these controls was 47.1 hours (IQR, 46.0 to 48.1 hours). In the comparison between cases and controls that were Mantoux positive in the Mantoux screening study, there was a trend for cases (n=15) who were Mantoux positive at the 30-day follow-up assessment to be younger than controls that were Mantoux positive (n=10) (median age 4

.0 months (IQR, 2.0 to 6 **.0 months)** **58**

in cases and 10.5

months (IQR, 5.0 to 13 **.0 months)** in controls; **P=0.** **58**

072). Cases included in the Mantoux screening sub-study had a 2.9-fold (95% CI, 1.09 to 7.84; P=0.035) greater odds of being Mantoux positive than were controls, after adjusting for age (in months). Despite the small sample size in this sub-study (38 cases and 56 controls: 94 participants), there was 100% power to detect the observed 21.6 percentage point difference in Mantoux positivity between cases screened at the 30-day follow-up appointment and controls. 6.4Synopsis of Chapter 6 This Chapter focussed on the procedures followed that aimed to establish a diagnosis of PTB in PERCH cases at the South African site. It also includes the findings of a small sub-study which evaluated Mantoux positivity in controls, compared to cases that underwent Mantoux testing at the 30-day follow-up appointment. Pertinent findings from these analyses include: I. Clinical disease severity (as evidence by lethargy and in-hospital mortality) of enrolled cases impacted negatively on completeness of IS specimen collection; II. In multivariate analyses, ward clinician decision making regarding submission of GAs for mycobacterial culture was prompted by; (a) Older age group, with a 2% increased adjusted odds of submission of GAs with each one month increase in age at admission; (b) Supporting clinical investigations, including: i. Positive HIV infection status; ii. Positive Mantoux response; III. 146 (15.9%) of the 920 South African PERCH

cases had a clinical or microbiologically- confirmed **diagnosis of** PTB, **of** **555**

which: (a) 27 (18.5%) were microbiologically-confirmed; (b) 119 (81.5%) were clinically suspected, without microbiologic confirmation; IV. Culture-confirmed PTB was observed in 27 (3.0%) of the 906 cases from whom at least one specimen was submitted for Mtb culture; V. The diagnostic yields of GA and IS specimens were equivalent amongst children hospitalised with CAP at the South African PERCH site; VI. Submission of a second IS specimen for Mtb culture enhanced the diagnostic yield by 33.3%. This had bearing on the other PERCH sites, which only submitted one IS specimen on their enrolled cases, and allowed for potential adjustment of the estimated FA of pneumonia associated with Mtb at each site; VII. In a small sub-study of Mantoux test positivity amongst cases (screened using Mantoux tests at the 30-day follow-up PERCH visit) and controls, cases (14/38; 36.8%) had a significantly greater adjusted odds of being Mantoux positive than were controls (10/56; 17.9%) (aOR 2.87; 95% CI, 1.09 to 7.84) after adjusting for age (in months). 7 Findings from the PLANS

South African Cases **This Chapter presents the characteristics of children** **794**

enrolled into the PLANS study at the South African PERCH site. As a starting point, data from the CHBAH mortuary database are presented for the PERCH study time frame and the time frame covered by PLANS. Thereafter, a descriptive analysis of the 38 children included in PLANS at the South African site is given followed by an appraisal of the completeness of capture of in-hospital deaths in the CHBAH Paediatric Admissions and Discharge Registry. 7.1CHBAH Mortuary Data PERCH commenced at the South African site on 17th August 2011 and the last case was enrolled on 31st August 2013. University of the Witwatersrand Ethics Committee permissions to commence on the PLANS substudy was granted on 17th September 2012 (see Appendix F) and children hospitalised with pneumonia through 31st December 2013 were eligible for inclusion into PLANS. Leaving a month of 'lag time' in which to accommodate paediatric admissions that may have died subsequent to their admission on 31st December 2013, meant that the mortuary database inclusive of individuals dying at CHBAH through 31st January 2014 was interrogated in order to assess the numbers of children dying during the conduct of PLANS (Figure 7.1). As the mortuary database does not contain accurate data on patient age or cause-of-death, the mortuary data were merged against the CHBAH Paediatric Admission and Discharge Registry in order to obtain these parameters. Strict criteria, using hospital numbers and date of death, were used which necessarily would have limited the degree of matching in the merge (due to transcription errors in hospital number and date of death). In this merge 80% of children matched to both the mortuary database and the CHBAH Paediatric Admission and Discharge Registry were age-eligible for PERCH (i.e., between the ages of one and 59 months at admission) and 35.0% (41/117) of the age-eligible children died of pneumonia (green boxes in Figure 7.1). Of the 252 children logged in the mortuary database as having died in the medical paediatric wards between 17th September 2012 and 31st January 2014 (the 'PLANS time frame'), 202 (80.2%) were imputed to be age-eligible for PERCH and 73 (36.1%) of the age-eligible children were imputed to have died from pneumonia (red boxes in Figure 7.1). 172 PERCH & PLANS Time Frame 16 865 deaths from 17/09/2011 to 31/01/2014 Merge to Paediatric Admission and Discharge Registry for Age Group and Cause of Death 16 093 adults 134 unassigned age group 633 paediatric patients 16 227 adults (inferred) PLANS Time Frame 638 paediatric patients (inferred) 97 (15.2%) paediatric matches to database 77 (79.4%) age-eligible for PERCH 9 651 deaths from 17/09/2012 to 31/01/2014 25 (32.5%) of 77 dying from pneumonia 9 210 adults 94 unassigned to age group 347 paediatric patients 9 301 adults (inferred) 350 paediatric patients (inferred) 50 (14.3%) paediatric matches to database 40 (80.0%) age-eligible for PERCH 252 (72.0%) medical paediatric deaths 16 (40.0%) of 40 dying from pneumonia 202 (80.2%) age-eligible for PERCH 73 (36.1%) age-eligible and dying from pneumonia Fig. 7.1: Mortuary Data Merged to the CHBAH Paediatric Admission and Discharge Registry to Estimate the Number of Age-eligible Children Dying from Pneumonia During the PLANS Enrolment Time Frame 173 7.1.1PLANS Cases South Africa contributed 38 (90.5%) of the 42 cases included in PLANS, with a further two cases each coming from Mali and Thailand. The 38 South African PLANS cases represent 52.1% (38/73) of the age-eligible cases dying from pneumonia at CHBAH during the PLANS study time frame. Of the 38 South African PLANS cases, 11 (28.9%) had been enrolled into PERCH ante-mortem, and therefore had a full complement of study-specific data available from which to infer pneumonia aetiology. Of the 27 children not enrolled into PERCH ante-mortem, 10 (37.0%) were admitted after hours, six (22.2%) were admitted subsequent to the PERCH enrolment time frame (after 31st August 2013), five (18.5%) were screening errors (children that were eligible for enrolment into PERCH, but not enrolled although screened), five (18.5%) were ineligible for enrolment into PERCH (the parents of two had refused consent for participation in PERCH, two were admitted on non-screening days, and one had been hospitalised within the preceding two weeks), and one child died en route to the hospital, although his two-month old twin bother was enrolled into PERCH on the following day and survived his hospitalisation episode. Eighteen (47.4%) of the 38 South African PLANS cases

were female, and the median age of the cases **was** 8.3 **months (IQR,** **718**

3.0 to 17.0 months). Age at death in children enrolled into PLANS was similar to the age at death amongst children enrolled into PERCH and dying in-hospital at the South African site (median 6.0 months; IQR, 3.0 to 10.0 months),

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P=0. 087. The median duration of hospitalisation was 3 days (IQR, 1 to 8 days),

and the median time to post-mortem biopsy was 29.6 hours (Range, 2.5 to 132.3 hours). Twenty (52.6%) of the 38 South African PLANS cases

were HIV-infected with a mean CD4+ T-lymphocyte percentage of 19.7 (SD, 14 .5%) (n=20) and 685

a median HIVVL of 6.31 log10 RNA copies/mL (IQR, 5.71 to 6.70 log10 RNA copies/mL) (n=14). CD4+ T-lymphocyte percentages were lower (mean 10.9%; SD 9.5%) and HIVVLs were greater (6.83 log10 RNA copies/mL; 95% CI, 6.57 to 6.94 log10 RNA copies/mL) in HIV-infected South African PERCH cases that died in-hospital but were not enrolled into PLANS,

P=0. 031 and P=0. 013, respectively. Six (33.3%) of the 18 HIV- 748

uninfected PLANS cases were HEU. 7.1.2FTDResp-33 Results from PLANS Cases Lung biopsies Thirty-one (81.6%) of the 38 South African PLANS cases had organisms detected on post-mortem lung biopsy core specimens on FTDResp-33 PCR testing, with a median of two organisms (Range, 0 to 8 organisms) detected. Sixteen organisms were detected on FTDResp-33 PCR testing of post-mortem lung biopsy specimens, including viruses (adenovirus, CMV, coronavirus OC43, coronavirus HKU1, human bocavirus, HMPV, parainfluenza virus 3 and RSV), bacteria (C. pneumoniae, H.

influenzae type b, non-type b H. influenzae, 949

K. pneumoniae,

M. catarrhalis , pneumococcus, and S. aureus) and the 981

fungal species P. jirovecii (Figure 7.2). The most frequently detected organism on FTDResp-33 testing was P. jirovecii, detected in 20 (52.6%) of 38 children, but CMV (n=14, 36.8%) and K. pneumoniae (n=13, 34.2%) also featured prominently in this analysis (Figure 7.2). Organisms detected on FTDResp-33 PCR testing of core lung biopsies at low Ct values (Ct ≤20, indicating high organism density in analysed specimens) included: adenovirus, CMV, K. pneumoniae , P. jirovecii and RSV (Figure 7.2). Of the five children with one pathogen detected on FTDResp-33 testing of lung biopsy tissue, three (Cases 22, 36 and 38) were positive for P. jirovecii (at Ct values ranging from 15.7 to 28.6), one (Case 28) was positive for pneumococcus (Ct 32.2) and one (Case 31) was positive for coronavirus HKU1 (Ct 39.2) (Table 7.1). Of eight children positive for two pathogens on FTDResp-33 testing of post-mortem lung biopsies, four (Cases 6, 10, 17 and 25) had dual detection of P. jirovecii (with Cts ranging from 14.8 to 20.6) and CMV (Cts 13.0 to 29.8), two (Cases 4 and 9) had P. jirovecii and K. pneumoniae co-detection, one (Case 33) had co-detection of P. jirovecii and non-type b H. influenzae and one (Case 35) had co-detection of P. jirovecii and HMPV (Table 7.1). Nine children tested positive for three pathogens on FTDResp-33 PCR testing of post-mortem lung biopsy material: two had pure-viral co-detection (one with CMV (Ct 16.6), parainfluenza virus 3 (Ct 26.6) and RSV (Ct 20.6) (Case 11)), and one with adenovirus (Ct 20.2), human bocavirus (Ct 31.2) and HMPV (Ct 28.8) (Case 30)), one had pure-bacterial co-detection (with K. pneumoniae (Ct 24.4), S. aureus (Ct 27.2) and non-type b H. influenzae (Ct 27.5) (Case 21)). Four had co-detection with P. jirovecii (one with pneumococcus and M. catarrhalis (Case 16), one with coronavirus OC43 and CMV (Case 19), one with adenovirus and K. pneumoniae (Case Fig. 7.2: FTDResp-33 Organism Cycle Threshold Densities in Post-mortem Lung Biopsies from South African PLANS Cases Organisms detected in post-mortem lung biopsies of children included in the PLANS study. ADENO = adenovirus; CMV = human cytomeg- alovirus; COR43 = coronavirus OC43; CORHKU = coronavirus HKU1; CPNEU = C. pneumoniae ; Ct = Cycle threshold; FTDResp-33 = FastTrack Diagnostics Respiratory Pathogens 33 assay; HBOV = human bocavirus;

HIB = H. influenzae type b; HINF = H. influenzae non -type 36

b; HMPV = human metapneumovirus; MCAT = M. catarrhalis ; PARA3 = parainfluenza virus type 3; PJP = P. jirovecii ; PNEU = S. pneumoniae ; RSV = respiratory syncytial virus; SAUR = S. aureus . 176 24) and one with CMV and K. pneumoniae (Case 26)) (Table 7.1). CMV and K. pneumoniae co-detection was also seen in Cases 27 and 32. Four children had four organisms detected on FTDResp-33 testing of post-mortem lung biopsy material. Two (Cases 8 and 37) had co-detection of parainfluenza virus 3 and K. pneumoniae. The lowest Ct value of detection in each case (indicating the highest density of pathogen in each specimen tested) were for adenovirus (Ct 19.7; Case 8), RSV (Ct 22.3; Case 12), RSV (Ct 15.7; Case 14) and K. pneumoniae (Ct 18.3; Case 37) (Table 7.1). Two children had five organisms detected on post-mortem lung biopsy PCR testing, and both had co-detection of non

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aureus on these specimens. The lowest Ct values in these two children were observed for non-type b H. influenzae (Ct 30.4; Case 20) and K. pneumoniae (Ct 21.1; Case 34) (Table 7.1). All three children with ≥6 organisms detected on FTDResp-33 testing of lung biopsy specimens had P. jirovecii -CMV co-detection, two (Cases 5 and 13) were HIV-infected and one (Case 15) was HEU (Table 7.1). NP/OP swabs of cases enrolled into PERCH ante-mortem In the 11 children that were enrolled into PERCH ante-mortem, all had results available from NP/OP FTDResp-33 testing conducted at enrolment. Two had adenovirus detected at levels greater than the cut-off that best distinguished between cases and controls and one of these (Case 8) also had adenovirus detected on post-mortem lung biopsy PCR testing (Table 7.1). CMV was detected in densities greater than the cut-off which best distinguished cases from controls on NP/OP PCR testing in five children (Cases 10, 17, 23, 27 and 31), and CMV was detected in lung biopsy specimens in three of these children (Cases 10, 17 and 27) at Ct values ranging from 26.2 to 31.6 in the lung biopsy specimens. Pneumocystis jirovecii was detected on NP/OP PCR testing in three of the 11 children (Cases 10, 17 and 22), and in PCR testing of lung biopsy core tissue in all three (Ct 14.9 to 15.8 in lung biopsy specimens). RSV, detected in two children that had undergone NP/OP sampling ante-mortem (8 and 14), as well as in the twin of a case that demised en route to hospital (Case 7), was detected on PCR testing of lung tissue samples in one of these children (Case 14) who also had histologic evidence of RSV pneumonia on post-mortem lung biopsy (Figure 7.3 (a) and (b)). Tab. 7.1: Organism Detection in PLANS Cases Case SexHIV Age Days in Interval NP/OP IS Culture Blood Right Lung Left Lung Organism Lung Biopsy Likely Strength Status (months) hospital to Biopsy (hours) PCRa Culture Biopsy Culture Biopsy Culture Visualised on Histology PCR Pathogen of Evidence 1 F Pos 27.0 22 46.0 Neg EFAE EFAE · · · · · · EFAE Weak 2 M Neg 59.0 13 51.0 Neg Neg Neg · · · · · · Unknown · · · 3 M Neg 5.0 1 79.0 Neg CoNS Neg · · · · · · Unknown · · · 4 F Pos 4.0 8 21.0 KPNE (ESBL) Neg Neg · · · KPNE, PJP KPNE Moderate 5 M Pos 20.0 0 17.0 ECOL, KPNE, CALB ECOL, KPNE, CALB · · · CMV, HINF, KPNE, MCAT, Possibly KPNE Moderate PJP, PNEU 6 M Pos 3.0 12 68.0 Neg Neg Neg CMV, PJP CMV, PJP CMV, PJP Strong 7 M Neg (HEU) 2.0 0 21.0 RSVb Negb Negb CoNS HINF · · · · · · HINF Moderate 8 F Pos 8.5 21 29.2 ADENO, HINF, RSV SAUR Neg EFAE EFAE · · · ADENO, CMV, KPNE, Possibly ADENO and Moderate PARA3 EFAE Continued on next page . . . 178 Case SexHIV Age Days in Interval NP/OP IS Culture Blood Right Lung Left Lung Organism Lung Biopsy Likely Strength Status (month s) hospital to Biopsy (hours) PCRa Culture Biopsy Culture Biopsy Culture Visualised on Histology PCR Pathogen of Evidence 9 F Neg (HEU) 10.0 4 82.5 PNEU EFAE, ECLO EFAE, ECLO, KPNE · · · KPNE, PJP Possibly PNEU and Moderate KPNE 10 F Pos 7.5 2 9.5 CMV, ABAU, CALB Neg CALB Neg PJP CMV, PJP CMV, PJP Moderate PARA1, PJP, PNEU, RHINO 11 M Pos 5.0 22 32.0 Neg Neg Neg CMV CMV, PARA3, CMV Moderate RSV 12 F Neg 2.5 3 89.0 Neg Neg Neg CMV CMV, HINF, CMV Moderate MCAT, RSV 13 F Pos 2.5 4 5.5 Neg Neg Neg CMV, PJP CMV, CPNEU, CMV, PJP Moderate KPNE, PJP, PNEU, RSV, SAUR Continued on next page . . . 179 Case SexHIV Age Days in Interval NP/OP IS Culture Blood Right Lung Left Lung Organism Lung Biopsy Likely Strength Status (month s) hospital to Biopsy (hours) PCRa Culture Biopsy Culture Biopsy Culture Visualised on Histology PCR Pathogen of Evidence 14 M Neg 2.0 8 10.2 COR43, RSV Neg Neg Contam. Neg RSV COR43, PJP, PNEU, RSV RSV Moderate 15 F Neg (HEU) 9.0 1 114.2 SAUR ECLO, ABAU, CALB PAER Fungal CMV, CPNEU, HINF, KPNE, MCAT, PJP, PNEU, SAUR Possibly SAUR and CALB Moderate 16 F Pos 16.0 0 6.2 PNEU, PVEV PAER Neg Neg Fungal MCAT, PJP, PNEU Possibly PAER Moderate 17 F Pos 17.0 7 2.7 CMV, PJP, SAUR CALB Neg Neg CALB CMV, PJP CMV, PJP CMV, PJP Strong 18 F Neg 8.0 5 27.0 Neg SCER Neg · · · · · · Unknown · · · 19 F Pos 3.0 4 91.0 Neg ECLO ECLO CMV, PJP CMV, COR43, PJP CMV, PJP Moderate Continued on next page . . . 180 Case SexHIV Age Days in Interval NP/OP IS Culture Blood Right Lung Left Lung Organism Lung Biopsy Likely Strength Status (month s) hospital to Biopsy (hours) PCRa Culture Biopsy Culture Biopsy Culture Visualised on Histology PCR Pathogen of Evidence 20 M Neg 13.0 5 55.2 SAUR SAUR Neg · · · HBOV, HIB, HINF, PNEU, SAUR Moderate SAUR 21 F Pos 58.0 1 22.0 FLUA, HINF, SAUR MRSA MRSA, KPNE MRSA · · · HINF, KPNE, SAUR SAUR (possibly Moderate precipitated by FLUA) 22 M Neg 2.8 16 52.0 PJP ABAU, ECOL, Neg Neg Neg PJP PJP PJP Strong CPARA 23 M Neg (HEU) 43.0 2 8.5 CMV, HMPV Neg CoNS Neg Neg · · · · · · Unknown Moderate 24 M Neg (HEU) 41.0 1 53.0 PNEU Neg Neg · · · ADENO, KPNE, PJP Possibly PNEU Moderate Continued on next page . . . 181 Case SexHIV Age Days in Interval NP/OP IS Culture Blood Right Lung Left Lung Organism Lung Biopsy Likely Strength Status (month s) hospital to Biopsy (hours) PCRa Culture Biopsy Culture Biopsy Culture Visualised on Histology PCR Pathogen of Evidence 25 F Pos 2.8 3 58.2 Neg Neg Neg CMV, PJP CMV, PJP CMV, PJP Strong 26 F Neg 4.8 2 22.7 CFRE Neg Neg PJP CMV, KPNE, CMV, PJP; Moderate PJP Possibly CFRE 27 M Pos 8.5 3 34.0 CMV KPNE (ESBL) CoNS Neg KPNE (ESBL) · · · CMV, KPNE, PNEU Possibly KPNE and Moderate CMV 28 M Neg 6.0 1 53.0 PNEU Neg CALB · · · PNEU PNEU Strong 29 F Neg 46.0 0 20.0 ADENO, HINF Neg GAS Neg · · · · · · GAS Moderate 30 M Pos 17.0 7 15.5 Neg CoNS Neg · · · ADENO, HBOV, HMPV Mixed viral (ADENO, Moderate HBOV, HMPV) Continued on next page . . . 182 Case SexHIV Age Days in Interval NP/OP IS Culture Blood Right Lung Left Lung Organism Lung Biopsy Likely Strength Status (month s) hospital to Biopsy (hours) PCRa Culture Biopsy Culture Biopsy Culture Visualised on Histology PCR Pathogen of Evidence 31 M Neg (HEU) 8.0 2 28.5 CMV, HBOV, Neg Neg SAUR Neg · · · CORHKU Possibly SAUR Moderate PVEV 32 M Pos 3.0 22 28.0 Neg CoNS CoNS · · · CMV, HBOV, KPNE Unknown · · · 33 M Neg 10.0 0 36.5 Neg Neg Neg · · · HINF, PJP Possibly PJP and HINF Moderate 34 F Pos 11.0 2 132.2 ECOL KPNE (ESBL) KPNE (ESBL) · · · HINF, HMPV, KPNE, MCAT, Possibly KPNE and Moderate SAUR ECOL 35 M Pos 19.0 1 52.7 Neg Neg Neg PJP HMPV, PJP PJP Moderate 36 M Neg 3.0 24 25.0 ECOL (ESBL) CoNS CoNS · · · PJP Possibly PJP and ECOL Moderate Continued on next page . . . 183 Case SexHIV Age Days in Interval NP/OP IS Culture Blood Right Lung Left Lung Organism Lung Biopsy Likely Strength Status (month s) hospital to Biopsy PCRa Culture Biopsy Culture Biopsy Culture Visualised on PCR Pathogen of (hours) Histology Evidence 37 M Pos 2.5 3 30.0 Neg

ECOL (ESBL), KPNE (ESBL) ECOL (ESBL), KPNE (ESBL) · · · HMPV, KPNE, PARA3, PJP Possibly KPNE Moderate 38 F Pos 18.0 4 2.4 Neg Neg Neg · · · PJP PJP Moderate a Only NP/OP PCR results positive for organisms according to the cut-off thresholds used in the FA analysis presented in Chapter 4 are presented here; b Case 7 demised en route to the hospital: his twin brother was recruited into PERCH and survived to hospital discharge – the surviving twin's NP/OP FTDResp-33 PCR, IS and blood culture results are included in this Table. ABAU = A. baumannii ; ADENO = adenovirus; CALB = C. albicans ; CFRE = C. freundii ; CMV = human cytomegalovirus; Contam. = contaminated; CoNS = coagulase negative staphylococcus; COR43 = coronavirus OC43; CORHKU = coronavirus HKU1; CPARA = C. parapsilosis ; CPNEU = C. pneumoniae ; ECLO = E. cloacae ; ECOL = E. coli ; EFAE = E. faecalis ; ESBL = extended spectrum β-lactamase; FLUA = influenza A; GAS = Group A β-haemolytic streptococcus; HBOV = human bocavirus; HEU = HIV-exposed, uninfected; HIB = H. influenzae type b; HINF = non-type b H.

influenzae ; HMPV = human metapneumovirus; IS = induced sputum; **KPNE** = K. **pneumoniae ; MCAT** = M. **catarrhalis** 32

; MRSA = methicillin resistant S. aureus ; Neg = negative; NP/OP = nasopharyngeal-oropharyngeal; PARA1 = parainfluenza virus 1; PARA3 = parainfluenza virus 3; PJP = P. jirovecii ; PNEU = S. pneumoniae ; Pos = positive; PAER = P. aeruginosa ; PVEV =

parechovirus/ enterovirus; RHINO = human **rhinovirus; RSV = respiratory syncytial virus;** 130

SAUR = S. aureus ; SCER = S. cerevisiae. Highlighted rows represent cases with insufficient histologic evidence of an underlying pneumonic process contributing to the cause of death. Table produced using the stargazer package in R [66]. 184 K. pneumoniae PCR testing on post-mortem lung-biopsy specimens There was good concordance between FTDResp-33 PCR K. pneumoniae testing and clinical isolation of K. pneumoniae from sputum, blood and post-mortem lung biopsy tissue culture (Table 7.1). In 13 cases positive for K. pneumoniae on post-mortem lung biopsy specimen PCR testing, one cultured K. pneumoniae on blood culture (Case 4), one cultured K. pneumoniae on a good-quality IS specimen (Bartlett score +1) as well as on the left lung biopsy core (Case 27), five cultured the organism on either one or both lung biopsies (right and/ or left) (Cases 5, 9, 21, 34 and 37), and one was positive for K. pneumoniae on lung biopsy PCR testing only with all other specimens being culture-negative (Case 13). Children culture positive for organisms other than K. pneumoniae but FTDResp-33 PCR positive for K. pneumoniae on lung biopsy specimens (n=5) included Case 8 (culturing S. aureus on IS and E. faecalis on right and left lung biopsies), Case 15 (culturing S. aureus on blood and A. baumannii , E. cloacae, P. aeruginosa and C. albicans on lung biopsy), Case 24 (positive for pneumococcus on blood culture), Case 26 (who cultured Citrobacter freundii on blood) and Case 32 (positive for coagulase negative staphylococci on lung biopsy cultures). Of the five cases culturing organisms other than K. pneumoniae on clinical specimens, but FTDResp-33 positive for K. pneumoniae on lung biopsy testing, two (Cases 15 and 26) cultured Gram-negative organisms and three (Cases 8, 24 and 32) cultured Gram-positives. In summary, amongst nine children (Cases 4, 5, 9, 15, 21, 26, 27, 34 and 37) positive for K. pneumoniae on lung biopsy PCR testing as well as culture-positive for Gram-negative bacterial organisms seven (77.8%) were positive for K. pneumoniae on culture of clinical specimens. 7.1.3Blood cultures in PLANS cases Eleven (28.9%) of the 38 children included in PLANS at the South African site had blood cultures positive with clinically significant isolates, with Gram-positive pathogens predominating (54.5%, 6/11) (Table 7.1). Three (Cases 9, 24 and 28: all HIV-uninfected) cultured pneumococcus and three (Cases 15, 20 and 21: two of whom were HIV-uninfected) cultured S. aureus. Gram-negative organisms isolated on blood culture included C. freundii (n=1; Case 26), E. coli (n=2; Cases 34 and 36) (one of which was

extended spectrum β-lactamase (ESBL) producing), K. pneumoniae 71

ESBL (n=1; Case 27) and P. aeruginosa (n=1; Case 16). A 58-month old HIV-infected girl, dying within one day of her

hospital admission, cultured **methicillin resistant Staphylococcus aureus (MRSA)** 71

on her blood culture and also tested positive for S. aureus, non-type b H. influenzae and influenza A on her NP/OP swab (Case 21). 7.1.4Histology in PLANS cases Representative histologic specimens (representing lung tissue of adequate quality to determine whether a child died from pneumonia or not, and what pathogens were likely responsible for the fatal pneumonia episode) were available for 36 (94.7%) of the 38 South African PLANS cases and of these, 29 (72.2%) had histologic evidence of pneumonia (Table 7.1). An offending pathogen was visualised on histology in 14 (48.3%) of the 29 cases with histologic evidence of pneumonia: dual CMV and P. jirovecii infection in five, P. jirovecii in four, CMV in two, fungal elements in two, and RSV in one. The histologic appearance of three of the cases (Case 11, 14 and 17), representing fatal CMV, RSV and P. jirovecii pneumonia, are shown in Figure 7.3. 7.2Inferred Aetiology Attributions for

PLANS Cases Using a parsimonious approach in the attribution of infectious aetiology to the PLANS cases according to the strategy described in Section 2.4.6, it was possible to assign a likely pathogen in 26 (89.7%) of the 29 PLANS cases that had sufficient histologic

evidence of pneumonia on post-mortem lung 978

biopsy with 'strong' evidence in five (19.2%), 'moderate' evidence in 20 (76.9%) and 'weak' evidence in one (3.8%) (Table 7.2). It is evident from this analysis that the pathogens most frequently implicated with mortality in children with histologically-confirmed pneumonia at the South African PERCH site included: • CMV in 10 (34.5%) of 29 cases; • P. jirovecii in 10 (34.5%) of 29 cases; • K. pneumoniae in 5 (17.2%) of 29 cases; • S. aureus in 3 (10.3%) of 29 cases; • Adenovirus in 2 (6.9%) of 29 cases; and • Pneumococcus in 2 (6.9%) of 29 cases. (b)(a) (c) (d) Fig. 7.3: Pathologic Changes Visualised on Post-mortem Lung Biopsies in Three PLANS Cases (a) Syncytium and debris at 200× magnification (Case 14): fatal RSV pneumonia; (b) Syncytia and debris at 400× magnification (Case 14): fatal RSV pneumonia; (c) Dense inflammatory infiltrate and alveolar spaces packed with foamy eosinophilic exudate in a case of fatal P. jirovecii pneumonia (Case 17) (200× magnification); (d) Typical owl's eye inclusion bodies in pneumocytes infected with CMV in a case of fatal CMV pneumonia (Case 11) (400× magnification). All images stained with haematoxylin and eosin stains. 187 Tab. 7.2: Organism Attribution in 29 PLANS Cases with Histologically- confirmed Pneumonia Strength of Evidence PathogenStrong Moderate Weak Unknown ADENO & EFAE 0 1 0 0 CMV 0 2 0 0 CMV & PJP 3 3 0 0 CMV & PJP & CFRE 0 1 0 0 EFAE 0 0 1 0 KPNE 0 2 0 0 KPNE & CMV 0 1 0 0 KPNE & ECOL 0 1 0 0 KPNE & PNEU 0 1 0 0 Mixed viral (ADENO, HBOV, HMPV) 0 1 0 0 PJP 1 2 0 0 PNEU 1 0 0 0 PAER 0 1 0 0 RSV 0 1 0 0 SAUR 0 1 0 0 SAUR & CALB 0 1 0 0 SAUR & FLUA 0 1 0 0 Unknown 0 0 0 3 Total 5 20 1 3 ADENO = adenovirus; CALB = C. albicans ; CFRE = C. freundii ; CMV = human cytomegalovirus; ECOL = E. coli ; EFAE = E. faecalis ; FLUA =

influenza A; HBOV = human bocavirus; HMPV = human metapneumovirus; KPNE = K. **pneumoniae** ; PJP = **P.** 370

jirovecii ; PNEU = S. pneumoniae ; PAER = P. aeruginosa ; RSV = respiratory syncytial virus; SAUR = S. aureus. Amongst children with 'strong' evidence to support an aetiologic diagnosis in their fatal pneumonia episode, CMV (n=3), P. jirovecii (n=4) and pneumococcus (n=1) were the pathogens associated with the illness (Table 7.2). In five children with a likely pathogen attribution of K. pneumoniae (Cases 5, 9, 27, 34 and 37), the length of hospitalisation ranged from zero to four days and the interval to post-mortem biopsy ranged from 17.0 to 132.2 hours. All cultured K. pneumoniae on post-mortem lung biopsy specimens and were also FTDResp-33 PCR positive for K. pneumoniae on lung biopsy specimens. Isolation of K. pneumoniae in these cases probably does not reflect nosocomial acquisition of the infection in view of the short duration of hospitalisation in the cases; however, overgrowth of bacteria contaminating the post-mortem lung biopsy may have contributed to the detection of this pathogen in lung tissue given the delayed sampling time. In HIV-uninfected children, of which there were 10 with histologically-proven pneumonia, the implicated pathogens included CMV (n=2; Cases 12 and 26, both of whom were HIV-unexposed), P. jirovecii (n=2; Cases 22 and 26, also both HIV-unexposed), pneumococcus (n=2), K. pneu- moniae

(n=1), RSV **(n=1) and** S. aureus **(n=2).** Three **of** 513

the HIV-uninfected children with histologically-proven fatal pneumonia were HIV-exposed: the aetiologic assignation in these children were pneumococcus and K. pneumoniae co-infection (Case 9), S. aureus and C. albicans co-infection (Case 15), and unknown aetiology (Case 23), respectively. Amongst HIV-infected children with histologically-confirmed fatal pneumonia (n=19), CMV (n=8), P. jirovecii (n=8), and K. pneumoniae (n=4) were the predominant pathogens assigned to the fatal pneumonia episode. Respiratory viruses associated with death

in HIV-infected children with histologically-proven **pneumonia** included adenovirus (n **=2;** 970

one of whom had mixed viral infection with human bocavirus and HMPV), and influenza A (associated with MRSA septicaemia) (n=1). 7.3 A Note on the Underrepresentation of In-hospital Deaths in the CHBAH Paediatric Admissions and Discharge Registry An interesting observation brought out by the analysis of the PLANS data, was the considerable lack of representation of paediatric medical deaths in the CHBAH Paediatric Admissions and Discharge Registry, as evidenced by the 15% match when merging the registry to the CHBAH mortuary database (using a strict merging strategy) (see Figure 7.1). This points to a likely lack of completeness of the CHBAH Paediatric Admissions and Discharge Registry as far as accurate recording of in-hospital deaths is concerned. In the Paediatric Admission and Discharge Registry, for the time period spanning PERCH enrolment, only 35 (0.9%) of 3 761 children hospitalised with LRTI were noted to have died in-hospital. Correcting for a potential under-representation of in-hospital deaths would imply a corrected CFR attributed to LRTI as being approximately 6.2% (233/3 761 cases) (assuming that the 35 recorded deaths represent 15% of the total number of in-hospital deaths). The in-hospital CFR in PERCH was 4.0% (37/920), significantly lower than the imputed pneumonia CFR for CHBAH

(odds ratio (OR) 0. 63; **95% CI, 0.** 45 **to 0.90).** 737

7.4Synopsis of Chapter 7 Pertinent findings from the analyses of the PLANS substudy, presented in this Chapter, include: I. The cases included in PLANS constituted a good proportion (52.1%) of age-eligible children dying of pneumonia during the study sampling time-period (17th September 2012 through 31st January 2014), indicating that the study is reasonably representative of the aetiology of fatal

pneumonia in children between the ages of one **and 59 months** 116

hospitalised at CHBAH during the study; II. Sixteen pathogens were detected in 31 (82.6%) of the 38 PLANS cases on FTDResp-33 PCR testing of post-mortem lung biopsy specimens, with P. jirovecii (n=20), CMV (n=14) and K. pneumoniae (n=13) being the most frequently-detected organisms; III. There was good concordance between K. pneumoniae detected on FTDResp-33 PCR testing of lung biopsy specimens, and bacterial culture; IV. Of the 38 PLANS cases, 29 (76.3%) had histologic evidence of pneumonia and 26 (89.7%) of these had sufficient evidence to assign a likely pathogen as being associated with the fatal pneumonia; V. CMV (34.5%), P. jirovecii (34.5%) and K. pneumoniae (17.2%) were inferred to be the pathogens most likely associated with pneumonia mortality in the 29 children with histologically- confirmed pneumonia; VI. An appraisal of the CHBAH Paediatric Admissions and Discharge Registry suggests that there is considerable under-capture of in-hospital deaths at the facility. When correcting for a likely under-count of in-hospital deaths, the CFR of PERCH age-eligible LRTI deaths at CHBAH was 6.2%, significantly higher than the CFR observed in PERCH (4.0%). 8 The

Utility of CMV **PCR on** Whole **Blood in Childhood Pneumonia** 216

Aetiology Diagnosis CMV has been implicated in case-status

in HIV-infected and HEU **children** hospitalised **with** acute **pneumonia in** 17

PERCH at the South African site (see Chapters 4 and 5), as well as in fatal pneumonia in children (even if HIV-unexposed) enrolled in PLANS (Chapter 7). PERCH used NP/OP swab FTDResp-33 PCR testing to compare pathogen profiles between cases and controls, but in a substudy conducted at the South African site, whole blood CMV PCR assays were done in children that tested positive for CMV on NP/OP swabs or IS in order to explore the utility of CMV PCR testing on whole blood to support a diagnosis of CMV pneumonia in cases. The findings of this substudy are presented in this chapter. 8.1Specimens Submitted for CMV Testing Specimens submitted from cases and controls for CMV testing are depicted in Figure 8.1. Overall, 910 (98.9%) cases had available NP/OP swab results and of these, 376 (41.3%) were FTDResp-33 PCR positive for CMV 1. Three-hundred, thirty-two (40.1%) of the 827 IS specimens collected from cases were positive for CMV on FTDResp-33 testing. There was good concordance

between NP/OP and IS specimens in terms **of** 18

their respective positivity rates for the CMV PCR test: McNemar's $\chi 2$ 0.58 (P=0.448). Of the 959 (99.5%) controls that had available NP/OP PCR results, 452 (47.1%) were positive for CMV on FTDResp-33 testing (Figure 8.1). Children with CMV-positive results on FTDResp-33 testing were prioritised for testing of CMV on whole blood, based on the rationale that children negative for the organism on testing of respiratory specimens would be unlikely to have CMV on whole blood at density cut-offs greater than or equal to the density cut-offs that best discriminated between cases and controls amongst those that were positive for CMV on respiratory specimens (see page 69). Four-hundred, ten (44.6%) cases and 387 (40.1%) controls had whole blood tested for CMV using the R-gene™ assay. Amongst cases with positive NP/OP FTDResp-33 CMV results (n=353), 209 (59.2%) tested positive for CMV 1 Note that this differs from the 45.9% case NP/OP PCR prevalence of CMV depicted in Figure 4.1 (which includes cases with radiologically-confirmed pneumonia only). 191 920 Cases 964 Controls 910 (98.9%) NP/OP swabs 827 (89.9%) IS samples 67 (67.7%) ETT samples (from 99 ventilated cases) 410 (44.6%) WB samples 959 (99.5%) NP/OP swabs 387 (40.1%) WB samples WB Pos above density cut-off in children with CMV Pos NP/OP swabs Cases: 122/353 (34.6%) Controls: 73/383 (19.1%) Pos: 376 (41.3%) Pos: 332 (40.1%) Pos: 31 (46.3%) Pos: 452 (47.1%) Neg: 534 (58.7%) Neg: 495 (59.9%) Neg: 36 (53.7%) Neg: 507 (52.9%) WB Pos & NP/OP Inferred (after density cut-off applied) Cases: 122/910 (13.4%) Controls: 73/959 (7.6%) N=387 WB Neg WB Pos NP/OP Neg 3 1 NP/OP Pos 155 228 Total 158 (40.8%) 229 (59.2%) N=825 IS Neg IS Pos NP/OP Neg NP/OP Pos 434 60 51 280 NP/OP versus IS WB Neg WB Pos Pos/Pos Pos/Neg Pos/ND 96 38 10 169 19 21 Neg/Pos Neg/ND Neg/Neg 34 4 1 14 3 1 Total 183 (44.6%) 227 (55.4%) McNemar's $\chi 2$ =0.58, P=0.448 WB Pos & NP/OP Pos Cases: 209/353 (59.2%) Controls: 228/383 (59.5%) WB Pos & NP/OP Inferred Cases: 209/910 (23.0%) Controls: 229/959 (23.9%) Fig. 8.1: CMV PCR Results From Different Specimens Collected from Cases and Controls at the South African PERCH Site CMV = human cytomegalovirus; ETT = endotracheal tube; IS = induced sputum; ND = not done; Neg = negative; NP/OP = nasopharyngeal-oropharyngeal; Pos = positive; WB = whole blood.192 on whole blood. A similar proportion of controls, positive for CMV on FTDResp-33 testing of NP/OP swabs, tested positive for CMV on whole blood (228/383; 59.5%) (Figure

8.1). One-hundred, twenty-two (34.5%) of the 353 cases and 73 (19.1%) of the 383 controls that had positive CMV NP/OP and whole blood results, had CMV whole blood positivity at thresholds greater to or equal to the density which best discriminated between cases and controls. Assuming that all untested children had lower densities of CMV on whole blood translated into an inferred prevalence of CMV in WB among cases of 13.4% (122/910) and 7.6% (73/959) in controls (Figure 8.1). 8.2Marginal & Conditional Odds Ratios of CMV Whole Blood Positivity in PERCH Cases Marginal and conditional odds ratios of CMV whole blood positivity are presented in Table 8.1, and indicate that after correcting for age (in months), season and all other pathogens (in the conditional analysis), CMV detected on whole blood at threshold densities greater to or equal than that which best discriminated between case and control

status was significantly associated with radiologically-confirmed pneumonia **in all** children except **the** 893

group of HEU children (for whom there was sufficient statistical power (0.98 for this analysis) to discern a 10.3 percentage point difference in prevalence between cases and controls). The highest association of CMV detected on whole blood was among

HIV-infected children (FA **0.** 25; **95% CI, 0.** 00 **to 0.** 29

34) (Table 8.1). 8.3Comparison of Clinical Characteristics of Cases and Controls Based on Clinical Severity of Illness in Cases When using a disease severity composite measure as defined in Section 2.4.7, whole blood CMV PCR was useful in distinguishing between cases and controls in HIV-infected children only. After adjusting for age (in months), CMV detected in whole blood above the cut-off density (2.69 log10 copies/mL; Table G.1) which best discriminated between HIV-infected cases with radiologically-confirmed pneumonia and controls was observed in 37.5% (33/88) cases and 14.7% (20/136) controls

(aOR 3. 58; **95% CI, 1.** 36 **to** 9.43), **P=0.** 331

009. CMV whole blood PCR also discriminated between HIV-infected cases with and without (8/27; 29.6%) 'severe composite' disease (aOR 2.71; 95% CI, 1.15 to 6.39) after adjusting for age (in months), P=0.022. Tab. 8.1: Marginal and Conditional Odds Ratios of CMV Prevalence in Whole Blood (Radiologically-confirmed Pneumonia) Study Group Casesa Controls Marginal

Odds Ratio (95% CI) b **P-** value FA **(95% CI)** Conditional **Odds Ratio (95% CI)** c **P-** value FA **(95% CI)** 3

Powerd All children 90/518 (17.4) 73/959 (7.6) 2.31 <0.001 0.10 2.80 <0.001 0.11 1.00 (1.65 to 3.23) (0.07 to 0.12) (1.82 to 4.28) (0.08 to 0.13) All HIV-uninfected 55/429 (12.8) 53/823 (6.4) 1.95 0.001 0.06 2.72 <0.001 0.08 1.00 children (1.30 to 2.92) (0.03 to 0.08) (1.65 to 4.50) (0.05 to 0.10) HIV-unexposed 26/244 (10.7) 37/579 (6.4) 1.64 0.071 · · · 3.01 0.001 0.07 0.94 children (0.96 to 2.81) (1.57 to 5.76) (0.04 to 0.09) HEU children 26/161 (16.1) 13/224 (5.8) 2.73 (1.33 to 5.60) 0.006 0.10 (0.04 to 0.13) 2.39 (0.90 to 6.33)e 0.079 · · · 0.98 HIV-infected 35/89 (39.3) 20/136 (14.7) 3.71 <0.001 0.29 2.83 0.047 0.25 1.00 children (1.87 to 7.36) (0.18 to 0.34) (1.01 to 7.92) (0.00 to 0.34) a Cases – children with radiologically-confirmed pneumonia; b Marginal odds ratios adjusted by age (in months) and season; c Conditional odds ratios adjusted by age (in months), season and all other pathogens; d Power of each conditional logistic regression analysis to detect the observed difference in prevalence of CMV on whole blood between cases and controls at a significance level of ≤0.05. Highlighted rows reflect instances in which organism was significantly associated with case status; e These analyses were conducted adjusting for all potential pathogens, including CMV as detected on NP/OP swabs – if re-analysed without adjusting for NP/OP detection of CMV, the conditional Odds Ratio for HEU children would be 3.53 (95% CI, 1.51 to 8.24), with an estimated FA of radiologically-confirmed pneumonia associated with CMV (as detected on whole blood) of 0.12 (95% CI, 0.05 to 0.14). Site-specific density threshold cut-off values were used for human cytomegalovirus (on whole blood) (please refer to Table G.1 for cut-off densities which were applied). CI = confidence interval; CMV = human cytomegalovirus; FA = 'fraction of association'; Table produced using the stargazer package in R [66]. 194 By using CMV PCR on whole blood, the fraction of pneumonia attributable to CMV amongst HIV-infected cases with 'severe composite' disease,

compared to controls, was 0. 23 **(95% CI, 0.** 923

08 to 0.28). 8.4Comparison of Clinical Characteristics of Cases and Controls Based on Clinical Severity of Illness and High-density of CMV on NP/OP Swabs in Cases This Section presents analyses after assigning likely CMV-related pneumonia to cases with 'severe composite' disease (as defined in Section 2.4.7), restricting to those cases with CMV NP/OP densities greater than or equal to the cut-off density derived through

leave-one-out cross validation in the ROC analysis 186

of CMV NP/OP densities observed in the cases with ‘severe composite’ disease (Tables 8.2 through 8.4). 8.4.1HIV-unexposed Children HIV-unexposed cases with ‘severe composite’ disease and high-density NP/OP carriage of CMV were significantly younger than all other cases (median 5.5 months (95% CI, 3

.0 to 9 .0 months) versus 6 .0 months (IQR, 2 .0 to 14 .0 months); P=0. 58

019) and controls (7

.0 months (IQR, 4 .0 to 15 .0 months); P=0. 58

007) and were also significantly more likely to be severely malnourished than either comparator group (Table 8.2). They were also more likely to have leukocytosis (58.7% compared to 42.1%; P=0.017) and serum CRP ≥40 mg/L (35.6% versus 25.1%; p=0.007) compared to all other cases (Table 8.2). The proportion of cases with ‘severe composite’ disease and high-level CMV NP/OP carriage with CMV whole blood above the cut-off threshold which best distinguished between cases and controls was greater than that observed in all other cases and controls (28.3% versus 5.3% and 6.4%, respectively) but was significant after adjusting for age (in months), season and all other pathogens only in the comparison between cases and controls (aOR 4.04; 95% CI, 1.59 to 10.25) (Table 8.2). The fraction of radiologically-confirmed pneumonia attributable to CMV (as detected on whole blood in children with ‘severe composite’ disease and high-density NP/OP CMV carriage) was 0.21 (95% CI, 0.10 to 0.26). 8.4.2HEU Children Similar to what was observed in HIV-unexposed children, in HEU cases with ‘severe composite’ disease and high-density NP/OP carriage of CMV were significantly younger than all other Tab. 8.2:

Demographic and Clinical Characteristics of HIV-unexposed Cases with and without 373

High-level NP/OP CMV Density, and Controls: HIV-unexposed Children A B C Comparison of Columns A & B Comparison of Columns A & C Cases with Severe Disease & High-level CMV All Other Cases Controls aOR

(95% CI) P-value aOR (95% CI) P-value NP/OP Densitya Age (months) (median, IQR) 68

5.5 (3.0 to 9.0) 6.0 (2.0 to 14.0) 7.0 (4.0 to 15.0) 0.95 (0.91 to 0.99) 0.019 0.94 (0.89 to 0.98) 0.007 Female (%) 22/46 (47.8) 192/415 (46.3) 303/579 (52.3) 0.93 (0.51 to 1.69) 0.823 0.86 (0.47 to 1.58) 0.634 WAZ >-2 30/46 (65.2) 329/412 (79.9) 555/576 (96.4) Ref · · · Ref · · · WAZ >-3 to ≤-2 1/46 (2.2) 47/412 (11.4) 16/576 (2.8) 0.45 (0.03 to 2.16) 0.436 1.11 (0.06 to 5.84) 0.923 WAZ ≤-3 15/46 (32.6) 36/412 (8.7) 5/576 (0.9) 9.72 (4.73 to 19.41) <0.001 44.67 (15.88 to 147.04) <0.001 HIV Neg 46/46 (100.0) 415/415 (100.0) 579/579 (100.0) CXR+ (%) 39/39 (100.0) 205/344 (59.6) · · · · · Severity Composite Measure (%) 46/46 (100.0) 141/415 (34.0) · · · · · Ever ventilated (%)b 12/46 (26.1) 20/141 (14.2) 2.07 (0.90 to 4.64) 0.080 Received Ganciclovir (%) 1/46 (2.2) 3/412 (0.7) 2.67 (0.13 to 21.56) 0.401 Leukocytosis (%) 27/46 (58.7) 174/413 (42.1) 2.14 (1.15 to 4.06) 0.017 Leukopaenia (%) 0/46 (0.0) 4/413 (1.0) · · · · · Thrombopaenia (%) 2/46 (4.3) 9/413 (2.2) 1.91 (0.28 to 7.78) 0.420 CRP ≥40 mg/L (%) 16/45 (35.6) 101/403 (25.1) 0/105 (0.0) 2.46 (1.25 to 4.70) 0.007 Continued on next page . . . 196 Tab. 8.2, continued from previous page . . . A B C Comparison of Columns A & B Comparison of Columns A & C Cases with Severe Disease & High-level CMV All Other Cases Controls

aOR (95% CI) P-value aOR (95% CI) P-value 179

NP/OP Densitya CMV NP/OP PCR above threshold (%)c 41/46 (89.1) 52/415 (12.5) 160/579 (27.6) 0.56 (0.39 to 0.79) 0.001 18.64 (6.15 to 56.54) <0.001 CMV WB PCR above threshold (%)d 13/46 (28.3) 22/415 (5.3) 37/579 (6.4) 1.35 (0.79 to 2.31) 0.278 4.04 (1.59 to 10.25) 0.003 CMV NP/OP and WB PCR above 13/46 (28.3) 9/415 (2.2) 22/579 (3.8) 1.36 (0.69 to 2.69) 0.376 6.52 (2.35 to 18.13) <0.001 threshold (%)c, d CMV WB density ≥4.1 log10 copies/mL (%)e 3/41 (7.3) 6/152 (3.9) 8/257 (3.1) 1.93 (0.63 to 5.93) 0.251 2.55 (0.38 to 17.02) 0.330 CMV WB density ≥3.47 log10 copies/mL (%)f 10/41 (24.4) 17/152 (11.2) 37/257 (14.4) 0.95 (0.51 to 1.80) 0.882 1.30 (0.44 to 3.89) 0.632 Died in Hospital (%) 1/46 (2.2) 10/414 (2.4) 0.89 (0.05 to 4.87) 0.909 a A severity composite measure was derived in which all cases dying in-hospital, or who were ventilated during their PERCH hospitalisation, or who were hospitalised for >5 days were assigned as having ‘severe disease’. All of those assigned as having severe disease according to this composite measure had radiologically-confirmed pneumonia. Additionally, in this analysis children assigned as having high-density NP/OP carriage of CMV had CMV density ≥4.77 log10 copies/mL (determined through

leave-one-out cross validation in the ROC analysis 186

of CMV NP/OP density in HIV-unexposed cases with or without 'severe composite' disease only); b Analysis restricted to cases with 'severe composite disease' only, so as to minimise bias amongst ventilated children; c The CMV NP/OP cut-off density which best distinguished cases from controls was 4.98 log10 copies/mL in HIV-unexposed children (see Table G.1); d The CMV whole blood cut-off density which best distinguished cases from controls was 3.33 log10 copies/mL in HIV-unexposed children (see Table G.1); e 4.1 log10 copies/mL is a putative cut-off density of CMV on whole blood which has been used to attribute an association of CMV with pneumonia in young children [226, 518]; f The whole blood density cut-off ≥3.47 log10 copies/mL for CMV reflects the density of organism which best distinguished between cases with 'severe composite' and those without 'severe composite' disease in HIV-unexposed children, and was derived through

leave-one-out cross validation in the ROC analysis, 186

using the Youden index.

aOR = adjusted odds ratio (odds ratio adjusted for age 351

(in months) in all analyses; for analyses of CMV on NP/OP and/ or whole blood, adjustment was also made for season and all other pathogens); CMV = human cytomegalovirus;

CRP = C-reactive protein; CXR+ = radiologically-confirmed pneumonia; HIV = human immunodeficiency virus 105

type 1; IQR = interquartile range; Neg = negative;

NP/OP = nasopharyngeal-oropharyngeal; PCR = polymerase chain reaction; 18

Ref = Referent;

ROC = receiver operating characteristic; WAZ = weight-for-age Z-score; 303

WB = whole blood; Table produced using the stargazer package in R [66]. 197 8. CMV Whole Blood Analysis198 cases and controls (median 4

.0 months (IQR, 3 .0 to 6 .0 months) versus 5 .0 months (IQR, 2 .0 to 11.0 months) 58

and 9.0 months (IQR, 4.0 to 16.5 months, respectively), and were significantly more likely than either comparator group to be severely malnourished (Table 8.3). They were also significantly more likely to have received ganciclovir (23.8% versus 5.1%; P=0.007) than all other cases (Table 8.3). The proportion of cases with 'severe composite' disease and high-density NP/OP CMV carriage with CMV whole blood densities above the cut-off threshold which best distinguished cases from controls was significantly higher than that observed in all other cases or controls (47.6% versus 11.4% and 5.8%, respectively) (Table 8.3). Of note, was that HEU cases with 'severe composite' disease and high-level NP/OP CMV density had a 9.47-fold (95% CI, 1.76 to 45.82) greater odds of dying in-hospital than did all other cases (Table 8.3). The fraction of radiologically-confirmed pneumonia attributable to CMV as detected on whole blood amongst HEU cases with 'severe composite' disease and high-density CMV NP/OP carriage was 0.40 (95% CI, 0.11 to 0.46). 8.4.3HIV-infected Children HIV-infected cases with 'severe composite' disease and high-density NP/OP carriage of CMV

were significantly younger, and were more likely to be severely malnourished, than 497

all other cases and controls (Table 8.4). The proportion of cases with 'severe composite' disease and high-density NP/OP CMV carriage with CMV whole blood density greater than or equal to the cut-off that best distinguished between cases and controls was also significantly greater (60.9%) than observed in all other cases (18.8%) and controls (14.7%) (aOR 2.71

(95% CI, 1.15 to 6.39) **and** 10.29 **(95% CI,** 2.81 **to** 37.65), **respectively)** 59

(Table 8.4). The FA of CMV detected on whole blood amongst HIV-infected children with 'severe composite' disease and high-density NP/OP CMV carriage was 0.55 (95% CI, 0.39 to 0.59). 8.5A Note on The Cut-off Value of 4.1 log10 for CMV in Whole Blood The published cut-off density level of CMV in whole blood (4.1 log10 copies/mL [226]) discrim- inated between cases with radiologically-confirmed pneumonia and 'severe composite' disease and controls when interrogating the entire cohort (9.7% (20/206) cases versus 3.6% (14/387) controls: aOR 3.53; 95% CI, 1.46 to 8.54), and HIV-infected children (19.7% (13/66) cases versus Tab. 8.3:

Demographic and Clinical Characteristics of HEU Cases **with and without** 'Severe Composite' Disease **with** 373

High-level NP/OP CMV Density, and Controls: HEU Children A B C Comparison of Columns A & B Comparison of Columns A & C Cases with Severe Disease & High-level CMV All Other Cases Controls aOR

(95% CI) P-value aOR (95% CI) P-value NP/OP Densitya **Age** (months) **(median, IQR)** 68

4.0 (3.0 to 6.0) 5.0 (2.0 to 11.0) 9.0 (4.0 to 16.5) 0.89 (0.79 to 0.97) 0.021 0.84 (0.73 to 0.93) 0.006 Female (%) 12/21 (57.1) 127/272 (46.7) 109/224 (48.7) 1.50 (0.62 to 3.75) 0.375 1.43 (0.57 to 3.73) 0.451 WAZ >-2 9/20 (45.0) 187/271 (69.0) 205/220 (93.2) Ref · · · Ref · · · WAZ >-3 to ≤-2 4/20 (20.0) 45/271 (16.6) 10/220 (4.5) 2.97 (0.78 to 9.57) 0.080 6.75 (1.57 to 26.01) 0.006 WAZ ≤-3 7/20 (35.0) 39/271 (14.4) 5/220 (2.3) 5.43 (1.84 to 15.48) 0.002 21.96 (5.45 to 100.17) <0.001 HIV Neg 21/21 (100.0) 272/272 (100.0) 224/224 (100.0) CXR+ (%) 20/20 (100.0) 141/234 (60.3) · · · · · · Severity Composite Measure (%) 21/21 (100.0) 113/272 (41.5) · · · · · · Ever ventilated (%)b 7/21 (33.3) 25/113 (22.1) 1.73 (0.59 to 4.70) 0.295 Received Ganciclovir (%) 5/21 (23.8) 14/272 (5.1) 4.93 (1.44 to 15.02) 0.007 Leukocytosis (%) 12/21 (57.1) 119/272 (43.8) 1.88 (0.76 to 4.79) 0.172 Leukopaenia (%) 0/21 (0.0) 3/272 (1.1) · · · · · · Thrombopaenia (%) 0/21 (0.0) 6/272 (2.2) · · · · · · CRP ≥40 mg/L (%) 5/21 (23.8) 64/266 (24.1) 0/40 (0.0) 1.55 (0.48 to 4.27) 0.420 Continued on next page . . . 199 Tab. 8.3, continued from previous page . . . A B C Comparison of Columns A & B Comparison of Columns A & C Cases with Severe Disease & High-level CMV All Other Cases Controls

aOR (95% CI) P-value aOR (95% CI) P-value 179

NP/OP Densitya CMV NP/OP PCR above threshold (%)c 21/21 (100.0) 49/272 (18.0) 37/224 (16.5) 1.41 (0.82 to 2.43) 0.212 · · · 0.995 CMV WB PCR above threshold (%)d 10/21 (47.6) 31/272 (11.4) 13/224 (5.8) 2.32 (1.09 to 4.91) 0.028 6.60 (1.31 to 33.31) 0.022 CMV NP/OP and WB PCR above 10/21 (47.6) 24/272 (8.8) 10/224 (4.5) 2.49 (1.07 to 5.79) 0.034 9.40 (1.61 to 54.73) 0.012 threshold (%)c, d CMV WB density ≥4.1 log10 copies/mL (%)e 0/19 (0.0) 2/97 (2.1) 1/57 (1.8) 0.23 (0.01 to 6.16) 0.374 · · · 0.999 CMV WB density ≥3.83 log10 copies/mL (%)f 1/19 (5.3) 4/97 (4.1) 1/57 (1.8) 1.54 (0.14 to 17.58) 0.724 2.59 (0.05 to 143.56) 0.633 Died in Hospital (%) 3/21 (14.3) 5/272 (1.8) 9.47 (1.76 to 45.82) 0.005 a A severity composite measure was derived in which all cases dying in-hospital, or who were ventilated during their PERCH hospitalisation, or who were hospitalised for >5 days were assigned as having 'severe disease'. All of those assigned as having severe disease according to this composite measure had radiologically-confirmed pneumonia. Additionally, in this analysis children assigned as having high-density NP/OP carriage of CMV had CMV density ≥5.89 log10 copies/mL (determined through

leave-one-out cross validation in the ROC **analysis** 186

of CMV NP/OP density in HEU cases with or without 'severe composite' disease only); b Analysis restricted to cases with 'severe composite disease' only, so as to minimise bias amongst ventilated children; c The CMV NP/OP cut-off density which best distinguished cases from controls was 4.53 log10 copies/mL in HEU children (see Table G.1); d The CMV whole blood cut-off density which best distinguished cases from controls was 2.53 log10 copies/mL in HEU children (see Table G.1); e 4.1 log10 copies/mL is a putative cut-off density of CMV on whole blood which has been used to attribute an association of CMV with pneumonia in young children [226, 518]; f The whole blood density cut-off ≥3.83 log10 copies/mL for CMV reflects the density of organism in whole blood amongst cases with 'severe composite' disease which best distinguished those with 'high level' NP/OP CMV density from those with 'low level' NP/OP CMV density in HEU children (both derived through leave-one-out cross validation in ROC analysis, applying the Youden index). The Youden index for CMV NP/OP density in HEU children was 5.89 log10 copies/mL.

aOR = adjusted odds ratio (odds ratio adjusted for age 351

(in months) in all analyses; for analyses of CMV on NP/OP and/ or whole blood, adjustment was also made for season and all other pathogens); CMV = human cytomegalovirus; CRP = C-reactive protein; CXR+ = radiologically-confirmed pneumonia;

IQR = interquartile range; Neg = negative;

Ref = Referent;

WB = whole blood; Table produced using the stargazer package in R [66]. 200 Tab. 8.4:

High-level NP/OP CMV Density, and Controls: HIV-infected A B C Comparison of Columns A & B Comparison of Columns A & C Cases with Severe Disease & High-level CMV All Other Cases Controls aOR

5.5 (3.0 to 9.0) 8.0 (3.0 to 18.0) 9.5 (4.5 to 20.5) 0.93 (0.88 to 0.97) 0.002 0.92 (0.86 to 0.96) 0.002 Female (%) 20/46 (43.5) 37/69 (53.6) 78/136 (57.4) 0.51 (0.26 to 0.98) 0.046 0.52 (0.26 to 1.06) 0.074 WAZ >-2 21/46 (45.7) 34/68 (50.0) 96/135 (71.1) Ref · · · Ref · · · WAZ >-3 to ≤-2 11/46 (23.9) 11/68 (16.2) 22/135 (16.3) 2.01 (0.84 to 4.65) 0.107 2.28 (0.91 to 5.62) 0.075 WAZ ≤-3 14/46 (30.4) 23/68 (33.8) 17/135 (12.6) 2.27 (1.02 to 4.99) 0.042 3.15 (1.32 to 7.56) 0.010 HIV Pos 46/46 (100.0) 69/69 (100.0) 136/136 (100.0) WHO Stage I (%) 0/46 (0.0) 3/69 (4.3) 60/136 (44.1) Ref · · · Ref · · · WHO Stage II (%) 1/46 (2.2) 2/69 (2.9) 3/136 (2.2) · · · 0.989 · · · 0.989 WHO Stage III (%) 13/46 (28.3) 15/69 (21.7) 22/136 (16.2) · · · 0.989 · · · 0.988 WHO Stage IV (%) 32/46 (69.6) 49/69 (71.0) 51/136 (37.5) · · · 0.989 · · · 0.988 CXR+ (%) 41/41 (100.0) 48/60 (80.0) · · · · · · Severity Composite Measure (%) 46/46 (100.0) 42/69 (60.9) · · · · · · Ever ventilated (%)b 10/46 (21.7) 4/42 (9.5) 1.50 (0.43 to 6.12) 0.540 Received Ganciclovir (%) 14/45 (31.1) 12/67 (17.9) 1.74 (0.69 to 4.45) 0.243 Continued on next page . . . 201 A B C Comparison of Columns A & B Comparison of Columns A & C Cases with Severe Disease & High-level CMV All Other Cases Controls

NP/OP Densitya Leukocytosis (%) 30/44 (68.2) 34/69 (49.3) 2.15 (0.95 to 5.03) 0.070 Leukopaenia (%) 2/44 (4.5) 6/69 (8.7) 0.88 (0.12 to 4.85) 0.891 Thrombopaenia (%) 8/45 (17.8) 9/69 (13.0) 1.39 (0.47 to 4.15) 0.548 CRP ≥40 mg/L (%) 16/45 (35.6) 23/67 (34.3) 1/27 (3.7) 2.03 (0.88 to 4.74) 0.099 10.93 (1.84 to 211.93) 0.030 CMV NP/OP PCR above threshold (%)c 37/46 (80.4) 10/69 (14.5) 25/136 (18.4) 2.94 (1.28 to 6.74) 0.011 54.19 (7.73 to 380.13) <0.001 CMV WB PCR above threshold (%)d 28/46 (60.9) 13/69 (18.8) 20/136 (14.7) 2.71 (1.15 to 6.39) 0.022 10.29 (2.81 to 37.65) <0.001 CMV NP/OP and WB PCR above 22/46 (47.8) 6/69 (8.7) 14/136 (10.3) 2.52 (0.96 to 6.59) 0.058 10.96 (2.82 to 42.57) <0.001 threshold (%)c, d Continued on next page . . . 202 A B C Comparison of Columns A & B Comparison of Columns A & C Cases with Severe Disease & High-level CMV All Other Cases Controls

NP/OP Densitya CMV WB density ≥4.1 log10 copies/mL (%)e 12/46 (26.1) 4/42 (9.5) 5/64 (7.8) 4.47 (0.97 to 20.65) 0.053 210.05 (6.88 to 6 410.41) 0.002 CMV WB density ≥2.29 log10 copies/mL (%)f 34/46 (73.9) 18/42 (42.9) 31/64 (48.4) 1.39 (0.51 to 3.79) 0.520 4.58 (0.82 to 25.52) 0.078 Died in Hospital (%) 8/46 (17.4) 9/69 (13.0) 1.27 (0.43 to 3.75) 0.666 a A severity composite measure was derived in which all cases dying in-hospital, or who were ventilated during their PERCH hospitalisation, or who were hospitalised for >5 days were assigned as having 'severe disease'. All of those assigned as having severe disease according to this composite measure had radiologically-confirmed pneumonia. Additionally, in this analysis children

assigned as having high-density NP/OP carriage of CMV had CMV density ≥4.99 log10 copies/mL (determined through

leave-one-out cross validation in the ROC **analysis** 186

of CMV NP/OP density in HIV-infected cases with or without 'severe composite' disease only); b Analysis restricted to cases with 'severe composite disease' only, so as to minimise bias amongst ventilated children; c The CMV NP/OP cut-off density which best distinguished cases from controls was 5.42 log10 copies/mL in HIV-infected children (see Table G.1); d The CMV whole blood cut-off density which best distinguished cases from controls was 2.69 log10 copies/mL in HIV-infected children (see Table G.1); e 4.1 log10 copies/mL is a putative cut-off density of CMV on whole blood which has been used to attribute an association of CMV with pneumonia in young children [226, 518]; f The whole blood density cut-off ≥2.29 log10 copies/mL for CMV reflects the density of organism in whole blood amongst cases with 'severe composite' disease which best distinguished those with 'high level' NP/OP CMV density from those with 'low level' NP/OP CMV density in HIV-infected children (both derived through leave-one-out cross validation in ROC analysis, applying the Youden index). The Youden index for CMV NP/OP density in HIV-infected children was 4.99 log10 copies/mL.

aOR = adjusted odds ratio (odds ratio adjusted for age 351

(in months) in all analyses; for analyses of CMV on NP/OP and/ or whole blood, adjustment was also made for season and all other pathogens); CMV = human cytomegalovirus;

CRP = C-reactive protein; CXR+ = radiologically-confirmed pneumonia; **HIV = human immunodeficiency virus** 105

type 1; IQR = interquartile range;

NP/OP = nasopharyngeal-oropharyngeal; PCR = polymerase chain reaction; Pos = **positive;** 376

Ref = Referent;

ROC = receiver operating characteristic; WAZ = weight-for-age Z-score; 303

WB = whole blood; WHO = World Health Organization; Table produced using the stargazer package in R [66]. 203 7.8% (5/64) controls: aOR 12.04; 95% CI, 1.77 to 81.85),

P=0. 005 **and P=0.** 010, **respectively.** Furthermore, **in the** 836

analysis of 'severe composite' disease in cases with high-density NP/OP CMV carriage amongst HIV-infected children, a density cut-off of 4.1 log10 copies/mL of CMV in whole blood discriminated between cases (12/46; 26.1%) and controls (5/64; 7.8%) (aOR 210.5 (95% CI, 6.88 to 6 410.41); Table 8.4). In all other analyses (including for all HIV-uninfected children, regardless of -exposure status, HIV-unexposed children and HEU children), the 4.1 log10 density cut-off failed to discriminate between cases with 'severe composite' disease (with or without high-density CMV NP/OP density) and controls. 8.6Synopsis of Chapter 8 This Chapter has presented the findings of CMV whole blood PCR testing as applied to the diagnosis of pneumonia associated with CMV in the PERCH cohort. Pertinent findings from the Chapter include: I. A description on the targeted testing of CMV whole blood PCR in South African PERCH participants, which resulted in a total of 1 869 cases and controls with CMV NP/OP results and available and/ or inferred CMV whole blood PCR results, including the rationale by which CMV whole blood PCR results – at cut-off densities above those which best distinguished between cases with radiologically-confirmed pneumonia and controls – were assigned, even though not all children with available CMV NP/OP results were tested for CMV on whole blood; II. Importance of the CMV whole blood PCR assay in 'fine tuning' the attribution of radiologically- confirmed

WHO-defined severe or very severe pneumonia, compared **to** 195

the NP/OP PCR assay (as shown in Table 8.1, and comparing to Tables 4.1 through 4.4); III. Significant associations of CMV whole blood PCR positivity above threshold densities which best discriminate between cases and controls in a subset of cases with high probability of CMV pneumonia amongst HEU, HIV-unexposed and HIV-infected children; IV. FA of pneumonia associated with CMV viraemia in children with

'severe composite' disease and high-density NP/OP CMV carriage: (a) HIV-unexposed children of 0.21 (95% CI, 0.10 to 0.26); (b) HEU children of 0.40

(95% CI, 0. 11 **to 0.** 46); (c) **HIV-infected children** of **0.** 55 **(95% CI, 0.** 39 **to 0.** 59). V. Limited utility of the published 4.1 log 10 copies/mL cut-off in attribution of case status in the context of PERCH, except in HIV-infected children with 'severe composite' disease and high-density CMV NP/OP carriage compared to controls. 9 Discussion PERCH was a state-of-the-art pneumonia diagnostic study designed to interrogate the aetiology of under-5

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childhood pneumonia in LMICs in **the era of** widespread **access to**

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bacterial conjugate vaccines, PMTCT and ART. The South African PERCH site contributed the largest complement of PERCH cases and controls (1 884 participants from the Soweto catchment area), and hence

made a substantial contribution to the PERCH **evidence base. In**

23

keeping with other multi-national studies of childhood pneumonia aetiology [288, 289], RSV was found to be the most important contributor to under-5 pneumonia aetiology amongst children with radiologically-confirmed disease in PERCH (AF 30.7%; 95% Credible Interval, 26.8% to 35.3%) [295]. At the South African PERCH site, RSV was associated with an FA of 0.28 (95% CI, 0.27 to 0.28) to the all-case 'aetiology pie' when comparing cases with radiologically-confirmed pneumonia to age-frequency matched controls (Table 4.1). The group of children experiencing the highest FA associated with RSV (0.33; 95% CI, 0.31 to 0.33) was HIV-unexposed children (Table 4.3), and RSV played a smaller but significant role (0.12; 95% CI, 0.10 to 0.12)

in contributing to the FA **of** radiologically-confirmed pneumonia **in HIV-infected children**

746

(Table 4.4), the group of children with the highest proportion (89/112, 79.5%) of radiologically-confirmed pneumonia (Table 3.3). This calls into question whether PERCH was in fact a truly representative pneumonia aetiology study, or whether it was rather a study of 'LRTI', including bronchiolitis aetiology. Indeed, current paediatric pneumonia case definitions stipulate that the case-definition of pneumonia should exclude the clinically distinct entity of bronchiolitis which is almost always precipitated by viral agents [519, 520]. The ubiquity of wheezing (a clinical feature associated with viral LRTI [521]) within the clinical framework of childhood pneumonia aetiology studies is well known: in EPIC and SARI – two

studies that interrogated **the aetiology of** LRTI **in children and**

559

adults – wheezing featured prominently (61.2% in EPIC [268] and 36.0% in SARI (personal communication, Dr Sibongile Walaza)) in children <5 years of age, and RSV featured foremost amongst the pathogens detected in children (in 37% and 26% of under-5s in EPIC and SARI, respectively) [242, 268]. Whereas GABRIEL initially listed as one of its exclusion criteria the phenomenon of wheezing in potential cases [522], the protocol had to be adjusted during the course of study conduct as exclusion of wheezing infants was compromising the number of patients being 206 enrolled at the study sites [289]. In the final analysis, the prevalence of wheezing amongst participants in GABRIEL was 19.3% [289]. Amongst hospitalised pneumonia cases <1 year of age in the Drakenstein study, wheeze was present in 62% of children [246]. In analysis of patient characteristics from all PERCH sites, wheeze was present in 31.7% of cases with radiologically-confirmed pneumonia [295], similar to the prevalence of wheeze seen in HIV- uninfected South African cases (29.0%; 122/421, page 97), but higher than that seen in HIV- infected cases (14.8%; 13/88, page 108). In the South African PERCH cohort, wheeze was present in 32.1% (288/898) of all cases, regardless of chest radiographic findings (data not shown). Researchers in Kenya raised concern that the pre-eminence of viral aetiologies in aetiology studies of hospitalised pneumonia in young children may reflect sampling bias because researchers would be more amenable to enrolling children with less severe respiratory disease into their studies, as reflected by lower CFRs in study participants than in the patient cohort as a whole [200]. There is evidence from the CHBAH Paediatric Admission and Discharge Registry that cases dying in-hospital tend to be under-represented (only 15% of such cases were matched to mortuary data using a strict merging strategy in this study: see Section 7.3), and that inferring LRTI-associated CFRs for the PERCH time frame would translate into a CFR of 6.2% in the Paediatric wards, significantly higher than the CFR (4.0%) observed in PERCH at the South African site. Hence, even in the South African setting, there is evidence to suggest a selection bias towards recruiting less ill children into PERCH. Discrepancies in CFR between children treated for pneumonia in the general paediatric wards and those enrolled in PERCH are conjectural, however, as National data on trends in CFR for hospitalised pneumonia in under-5s was 4.1% in 2011/2012 [300]. 9.1RSV the 'High Hanging' Fruit Metanalyses

describing the ‘top three’ childhood pneumonia pathogens – S. pneumoniae , H. influ- enzae, and RSV – indicate that the largest burden of under-5 LRTI is caused by RSV (33.8 million (95% CI, 19.3 to 46.2 million) illness episodes in under-5s in 2005) approximately 10% of which are severe enough to warrant hospitalisation [285]. Although pneumococcus and Hib are responsible for a greater burden of severe disease necessitating hospitalisation (14.5 million (Uncertainty Range, 11.1 to 18.0 million) and 8.1 million (Uncertainty Range, 7.3 to 13.2 million), respectively [283, 284]), the combined numbers of severe pneumococcal and Hib disease fall far short

of the burden of RSV **disease.** Realisation of **the burden of** **107**

illness attributed to RSV has invigorated efforts into vaccine discovery, in order to establish a safe, cost-effective and efficacious preventive measure that will protect infants from developing severe RSV disease. Such interventions remain elusive to date, however. Efforts at RSV vaccine discovery were curtailed in the late 1960s after a trial of

a formalin- inactivated RSV vaccine, in which receipt of **the** vaccine **was** associated **with** **809**

more severe RSV disease (16/20 (80%) hospitalised amongst vaccinees versus 1/21 (5%) hospitalised amongst those that received parainfluenza virus but not formalin-inactivated RSV vaccine), prolonged hospital stay (mean 10.5 versus 6.7 days in the two groups, respectively), and two fatal outcomes (CFR 10.0%) [523, 524]. At present, the only effective – but prohibitively expensive – intervention

for the prevention of RSV disease **in high-risk infants,** is use **of** **484**

monoclonal antibody immuoprophylaxis which cannot feasibly be up-scaled for use in LMICs [525]. Newer strategies, such as vaccinating expectant mothers in the antenatal period as has been found

to be efficacious in preventing severe influenza-associated **disease in** **549**

their infants [526, 527], may be an alternative strategy of eliciting protective immunity against RSV in infants [528].

Candidate vaccines have been found to be safe and **immunogenic in** **484**

non-pregnant females [529, 530], and at the time of writing, the first Phase 3 clinical trial of vaccination targeting RSV in pregnant women is underway [531]. Incidence rates of pneumonia attributable to RSV were high in this study, particularly in children <12 months of age (in which RSV-associated pneumonia incidence rates were >1 000 per 100 000 children for all groups tested) (Table 5.2). The highest incidence rate (1 959.3; 95% CI, 1 812.3 to 2 115.0

per 100 000 children) was observed in HEU **children,** **838**

who also

had a significantly **higher** relative **risk of** RSV pneumonia **compared to HIV-** unexposed **children (RR** 1.50; **95% CI, 1.** **447**

30 to 1.73) (see Table 5.2). Furthermore, in

children between the ages of one **and** 59 **months,** HIV-infected **and** **259**

HEU children had significantly greater RSV-associated pneumonia incidence rates than did HIV-uninfected and -unexposed children (RRs 1.66

(95% CI, 1. 19 **to 2.** 30) **and 1.** 38 **(95% CI, 1.** 24 **to 1.53), respectively)** **599**

(see Table 5.2). Cohen et al [363] reported on the pathogen-specific incidence rates of

pneumonia in children<6 **months of age** enrolled **in the** SARI **study,** **526**

demonstrating exceedingly high incidence rates of

RSV in HIV, HEU and HIV- unexposed children with significantly higher incidence 160

rate ratios

of RSV-associated LRTI in HIV-infected and HEU children 160

compared to HIV-unexposed infants (IRR 1.9

(95% CI, 1.3 to 2.7) and 1. 4 (95% CI, 1. 3 to 1.6), respectively). 609

In a study by Moyes et al [228], HIV infection was also associated with 41

significantly higher incidence rates of hospitalisation for ALRI in which RSV was detected using molecular techniques (12 800 (95% CI, 10 400 to 15 700)

per 100 000 children<12 months of age) compared to 564

HIV-uninfected children (2 400 (95% CI, 2 200 to 2 600) per 100 000 children <12 months of age) in children resident in Soweto in 2010 (RR, 5.4; 95% CI, 4.4 to 6.8). Foundational work on RSV-associated LRTI in African children highlighted

that HIV-infected children were more likely to develop 1

bronchopneumonia in the face of RSV infection compared to HIV-uninfected children who tended to present classically with bronchiolitis [164], a feature borne out in a more recent study from Pretoria [532]. Additionally, HIV-infected children hospitalised with RSV pneumonia had bacterial co-infection (as evidenced by higher prevalence rates of high-grade pyrexia, leukocytosis and bacteraemia) significantly more frequently than did HIV-uninfected children [164]. The

incidence (per 100 000) of RSV -associated severe LRTI in HIV-infected and -uninfected children 132

between the ages of two and 23 months of 259

age was 1 444 and 309, respectively in a study conducted at CHBAH in 1997/8 [159]. A further study, conducted in Soweto during the randomised controlled trial (RCT) of PCV9 in the late-1990s to early 2000s, estimated the incidence (per 100

000 children under-5 years of age) of 364

LRTI hospitalisation precipitated by RSV to be 4 500 and 1 940

in HIV-infected and -uninfected children, respectively [187]. Furthermore, HIV-infected 163

children testing positive for RSV during their pneumonia hospitalisation had a 13-fold (95% CI, 3.9 to 41.4) greater CFR than did HIV-uninfected children [187]. Although incidence rates of RSV hospitalisation in the early Soweto studies and SARI do not take

into consideration the background prevalence of RSV in the population (through using a 862

case-control approach), as has been demonstrated in PERCH the burden of RSV positivity was almost entirely concentrated in the cases (see Figures 4.1 through 4.4); hence using an attributable fraction method would not have been anticipated to 'dial down' the RSV-associated pneumonia incidence rates to a great extent, except, perhaps in the HIV-infected group (in whom case prevalence of RSV was not as high as that seen in HIV-uninfected children). The much higher RSV-associated incidence rates observed in the PCV9 and SARI studies may in part be due to different methodologies used in deriving the incidence rates (including recurrent RSV episodes in the PCV9 RSV study, and interrogating the youngest age group in the SARI study). Furthermore, the wider spectrum of illness – not solely confined to

WHO-defined severe or very severe pneumonia, as was **the case** 344

in PERCH – may have inflated RSV-associated incidence rates in the PCV9 RSV incidence study [187], SARI and the study conducted by Moyes et al [228]. Incidence rates of RSV-associated

severe or very severe pneumonia requiring hospitalisation **in** the **PERCH** 969

South Africa cohort (490.0 (95% CI, 475.1 to 505.2) per 100 000 population <5 years of age: Table 5.2) were, however, commensurate with rates derived from a recent meta-analysis of RSV-associated hospitalisation, in which it was estimated that 437 (95% Credible Interval, 298 to 642)

per 100 000 children <5 years of age 339

are hospitalised with RSV pneumonia annually [533]. 9.2Predominance of Viral Pathogens in Pneumonia Pathogenesis 9.2.1The Entire South African PERCH Cohort and HIV-uninfected Children Respiratory viral pathogens were associated with hospitalisation for WHO-defined

severe or very severe pneumonia in **the majority of** South African PERCH **cases** 749

with radiologically-confirmed disease (FA 0.59; 95% CI, 0.47 to 0.62) (Section 4.2.5). Furthermore, in HEU and HIV-unexposed children with radiologically-confirmed pneumonia, respiratory viral pathogens collectively were associated with FA of 0.53

(95% CI, 0. 39 **to 0.** 58) **and 0.57 (95% CI, 0.** 43 **to 0.61) respectively** 579

(Figure 4.6). This finding is commensurate with other recent studies of child pneumonia aetiology utilising molecular diagnostic techniques [242, 268, 274–280], and echoes the literature spanning the 1960s through 1980s in which the pre-eminent role of viral agents in childhood pneumonia was emphasised [523, 534, 535]. In an early editorial piece, it was speculated that adenovirus, influenza, the parainfluenza viruses and RSV could constitute 60% of the aetiology in hospitalised cases of childhood pneumonia [534]. Amongst HIV-uninfected children, a wide spectrum of respiratory viruses were associated with case status, and these spectra differed to some extent between HEU and HIV-unexposed children (Figure 4.5). Adenovirus, coronavirus NL63, human rhinovirus,

influenza A and RSV were associated with radiologically-confirmed pneumonia **in** 402

HEU children (Table 4.2), while adenovirus,

HMPV, human bocavirus, **influenza A and B, parainfluenza virus types 1 and 3 and RSV** 133

featured amongst cases with radiologically-confirmed pneumonia in the HIV-unexposed group (Table 4.3). Rates of disease associated with adenovirus

(RR, 1. 93; **95% CI, 1.** 59 **to 2.** 34), influenza A **(RR, 1.** 98; **95% CI, 1.** 55 **to** 2 **.53)** and RSV **(RR, 1.** 38; **95% CI, 1.** 24 **to 1.** 89

53) were significantly greater in HEU children compared to HIV-unexposed

children between one **and 59 months of age**

982

(Table 5.2). Weinberg

et al [536] observed that HEU infants had significantly lower serum concentrations of 717

maternally-derived antibody to

influenza A and parainfluenza virus types 1-3 113

at birth than did HIV-unexposed infants, which on follow-up was noted to be associated with significantly higher seroconversion rates to – indicative of previous disease caused by – the parainfluenza viruses at six months of age. It is feasible that similar mechanisms (poor maternally-derived immunity to respiratory viruses, leading to increased susceptibility to circulating respiratory viruses) may predispose HEU infants to significantly higher rates of adenoviral and influenza A infections, as observed in the PERCH South African cohort. In the cohort of SARI HEU children hospitalised with LRTI at CHBAH, the relative risk of ARI hospitalisation associated with adenovirus and influenza

were 1.2 (95% CI, 1.0 to 1.6) and 1.2 (95% CI, 0. 8 to 1. 8), respectively 493

[363]. 9.2.2HIV-infected Children In contrast to the picture seen in HIV-uninfected children described above, respiratory viruses

were associated with radiologically-confirmed pneumonia in only FA of 472

0.22

(95% CI, 0. 10 to 0. 24) of HIV-infected children, 29

amongst whom opportunistic pathogens (CMV and P. jirovecii) were the predominant organisms associated with radiologically-confirmed pneumonia (FA 0.58; 95% CI, 0.38 to 0.65) (Figure 4.6). The only respiratory viruses significantly associated with case-status in HIV-infected children with radiologically-confirmed pneumonia were parainfluenza virus 3 and RSV (Figure 4.5), for which organism-specific incidence

rates (per 100 000 children in the one to 59 month age group) 368

were 671.8 (95% CI, 617.7 to 729.3) and 836.2 (95% CI, 768.9 to 907.8), respectively (Table 5.2). Parainfluenza virus type 1 was also associated with case-status

in a small proportion of HIV-infected children with very severe pneumonia, 534

regardless of chest radiographic findings (Figure 4.10). Additionally, human rhinovirus was associated with case-status amongst HIV-infected

children with very severe pneumonia in 987

whom there was radiologically-confirmed disease (Figure 4.10). The relative risk for parainfluenza virus type 3 infection in HIV-infected children was 7-fold (95% CI, 5.16 to 9.83) greater than those that were HIV-uninfected, substantially greater than the relative risk of RSV-associated pneumonia (Table 5.2). This relative risk mirrors closely the combined relative risk of parainfluenza virus type 1-3 disease observed in

HIV-infected compared to HIV-uninfected children in Soweto in the pre-ART era 132

(8.46; 95% CI, 4.95 to 10.47) [159]. In the pre-ART era, HIV-infected children with parainfluenza virus types 1-3 associated-LRTI had longer hospitalisation and significantly higher mortality rates than were observed in HIV-uninfected children [169]. Associations between human rhinovirus infection and pneumonia

in HIV-infected children have been observed in sub-Saharan Africa 5

[532, 537, 538], including children hospitalised at CHBAH [539]. Stratification by ART access in HIV-infected children Of importance in the analyses presented herein, is the variant pathogen association observed

in HIV-infected children dependent on whether they had accessed ART or not 518

prior to having been enrolled into PERCH. HIV-infected children on ART presented with RSV as being the single infectious agent statistically associated with case-status in those with radiologically- confirmed pneumonia (see page 133). Time on ART was not statistically dissimilar in cases with radiologically-confirmed pneumonia and controls in the

HIV-infected children that were on ART at the time of 80

enrolment into the study. In contrast, P. jirovecii was the only pathogen associated with case-status, amongst those with radiologically-confirmed disease, in ART-na¨ıve HIV-infected children. This

highlights the importance of ART as a means of reconstituting the immune system 789

in HIV-infected children, so as to protect them from illness precipitated by opportunistic pathogens [540, 541]. Contrasting Findings Among PERCH HIV-infected Children Compared to Other Studies Calder and Qazi [542] reviewed the evidence base of pneumonia aetiology studies in HIV- infected children in LMICs, concluding that bacterial pathogens are the most important agents precipitating hospitalisation for pneumonia in these children. Their review was based on 13 observational studies that compared

HIV-infected to HIV-uninfected children hospitalised with pneumonia, 549

and summarised blood culture and respiratory secretion culture results as follows: pneumococcus (7.4%) and S. aureus (2.4%)

were the most commonly isolated blood culture isolates in HIV-infected children; S. 904

aureus predominated over pneumococcus, and Klebsiella spp.

were the most frequently isolated Gram negative pathogens, in two studies 35

which reported on IS culture; CMV, RSV and influenza virus were the most prevalent viral pathogens identified on respiratory specimens; and detection of P. jirovecii was substantially more frequent

in HIV- infected children [542]. Of note in this review, was that most of the 806

included studies had been conducted in the 1990s and early 2000s and in settings in which bacterial conjugate vaccines and access to ART were either not available or extremely limited [542]. A strength of the approach used in PERCH was to adopt

a case-control study design in order to 961

adjust case FTDResp-33 PCR results against those of healthy controls. A limitation of PERCH was that the comparator sample (NP/OP swabs) – a highly imperfect proxy measure of lung secretions sampling – was the only feasibly available specimen for case-control analyses. Despite these strengths and failings, it was the opportunistic pathogens and respiratory viruses which were significantly associated with case status in HIV-infected children in PERCH – markedly divergent from the findings of Calder and Qazi [542]. This may reflect the era in which PERCH was conducted, in which access to HibCV, PCV and ART was well-established. 9.2.3Brief Notes on Adenovirus, HMPV, Influenza virus, Human Bocavirus and Human Rhinovirus Adenovirus, HMPV and influenza virus featured as important aetiologic agents amongst HIV-uninfected children enrolled at the South African PERCH site, but not in HIV-infected children. Furthermore, two viruses – human bocavirus and human rhinovirus – did not feature prominently in the analysis of

pneumonia aetiology in the cohort (Figure 4.5) until interrogated by stratifying according to pneumonia severity (Figure 4.10). These pathogens are discussed briefly here. Adenovirus, HMPV and Influenza virus Within the framework of PERCH, both the marginal and conditional logistic regression models failed to demonstrate an association between adenoviral (at cut-off densities which best distin- guished between cases and controls), HMPV or influenza virus detection in NP/OP swabs in HIV-infected children at the South African site (Table 4.4). Statistical power to detect signific- ance in these analyses amongst HIV-infected children (0.34, 0.15, 0.09 and 0.06 for adenovirus, HMPV, influenza A and influenza C virus, respectively; data not shown) were compromised by the relatively small sample size, however. Adenovirus and influenza viruses were associated with case-status in both HEU and HIV-unexposed

children, and HMPV **was associated with** case-status **in HIV-** **983**

unexposed children (Tables 4.2 and 4.3).

Adenovirus has been highlighted **as a cause of** severe **pneumonia in South African** **338**

children, with requirement for ICU admission (OR 8.3; 95% CI, 2.3 to 29.0) and concomitant bacteraemia (OR 11.2; 95% CI, 2.3 to 54.1) being independent risk factors for adenoviral pneumonia mortality [543]. The low prevalence of HIV-infection observed in that cohort (6.7%; 14/206) – retrospectively selected on the basis of a positive laboratory result for adenovirus – was attributed to better strategies aimed at preventing HIV infection in the community [543]. A study from Mozambique (which did not include RSV amongst the panel of pathogens tested) noted adenovirus infection as being the only viral agent that was significantly associated with hospitalisation with a 3-fold (95% CI, 1.38 to 8.12) higher prevalence amongst hospitalised children compared to non- hospitalised children with ARI, although results were not presented stratified by HIV-infection status [544]. In another Mozambican observational study, which did not employ a case-control approach, adenoviral-associated pneumonia incidence rates were 5.0- to 15.1

-fold higher in HIV- infected children **compared to** those that were **HIV-uninfected** **34**

[210], similar to the relative risk of disease (15.07; 95% CI, 6.62 to 34.33) observed by Madhi

et al [159] **in a study** from Soweto **conducted in the** **172**

late 1990s. Madhi et al [545] also observed a 5-fold (95% CI, 3.5 to 7.5)

higher incidence of HMPV-associated **LRTI** hospitalisation **in HIV-infected compared to -uninfected children in** **10**

Soweto. In the SARI study, however, HMPV-associated LRTI hospitalisation was similar in

HIV-infected and HIV- uninfected infants (RR **1.** 0; **95% CI, 0.** 6 **to 1.** **261**

6) with a roughly four-fold greater incidence rate of HMPV-associated LRTI in under-5s (653.3

(95% CI, 602 **.2 to** 707.6) **per** 100 **000 person years)** **947**

than was observed in PERCH (154.6 (95% CI, 147.4 to 162.0) per 100 000 children; Table 5.2) [546]. Healthy controls were not evaluated as a comparator group, which limited the ability to infer the contribution of HMPV to LRTI aetiology in the SARI study [546]. In a re-analysis of archived clinical samples from the Soweto PCV9 clinical trial participants, both adenovirus and HMPV were detected with

significantly lower prevalence **in HIV-infected compared to HIV-uninfected children** **5**

that had been hospitalised with LRTIs at CHBAH (aOR 0.27

(95% CI, 0. 09 **to 0.** 79) **and 0.** 31 **(95% CI, 0.** 18 **to 0.** 53), **respectively)** **210**

[539]. Significantly lower prevalence rates of these viruses in HIV-infected children from the pre-ART era is intriguing, and may reflect the importance of an intact host immune response in contributing to the manifestations of clinical illness in LRTI precipitated by these respiratory viral pathogens [547]. Influenza has been associated with an attributable fraction-adjusted prevalence of 5.3% in

children under- 5 **years of age hospitalised** with **severe** ARI **in the** SARI **study** **724**

between 2012 and 2016 [548], which is similar than that observed in the PERCH South African cohort overall (4.9%), for influenza A and B combined (Table 4.1). Hospitalisation with influenza-associated LRTI clusters particularly amongst individuals at

the extremes of age (<1 year and>65 **years)** and **in** **776**

HIV-infected persons [548, 549]. In vivo experimental models in mice indicate that preceding

respiratory viral infection may predispose to bacterial pneumonia **913**

through multiple mechanisms, and influenza virus is the prototype pathogen in this important clinico-pathological pathway [282]. Strategies aimed at immunising mothers against influenza in the antenatal period have been shown, using

a vaccine-probe approach, to significantly decrease **the burden of** **116**

all-cause LRTI hospitalisation in young infants [550], which underpins the importance of interventions to prevent influenza as a means of decreasing the burden of LRTI in children. Human Bocavirus Human bocavirus was associated with very severe pneumonia in the cohort as a whole, HEU children and HIV-unexposed children (Figure 4.10). In a study from Spain, human bocavirus was noted to be the fourth most prevalent virus associated with hospitalisation for LRTI in children, after RSV, human rhinovirus and adenovirus [551], and in a meta-analysis of respiratory virus-associated CAP in children it was noted to be the third most prevalent organism (after human rhinovirus and RSV) [552]. Human bocavirus has also been identified in 34%

of children <6 years of age hospitalised **with severe** **833**

ARI in China [553]. In children enrolled into the EPIC study, in whom no identified pathogen was identified in the primary analysis, human bocavirus was detected in 18.6% cases compared to 2.2% controls using RNA sequencing and Pan-Viral Group PCR (aOR 9.1; 95% CI, 1.6 to 103) [554]. Detection of human bocavirus messenger RNA, but not DNA, was significantly associated with case status in the EPIC study, lending further support for its role as an important pathogen in childhood pneumonia [555]. Human Rhinovirus Although skepticism over

the role of human rhinovirus **in the aetiology of** childhood **pneumonia** **879**

has been raised [556], the organism has been associated with under-5 CAP in numerous studies, including EPIC, GABRIEL, PERCH and SARI [242, 268, 289, 295]. At the PERCH South African site, human rhinovirus was associated with radiologically-confirmed pneumonia in the entire cohort (FA 0.06;

95% CI, 0. 04 **to 0.** 07) **and** HEU **children** (FA **0.** 08; **95% CI, 0.** 04 **to 0.** **399**

09) (Figure 4.5). Furthermore, human rhinovirus was associated with radiologically-confirmed disease in children presenting with features of very severe pneumonia in the entire cohort (FA 0.09; 95% CI, 0.06 to 0.10), HEU children (FA 0.11; 95% CI, 0.04 to 0.12), HIV-unexposed children (FA 0.04;

95% CI, 0. 00 **to 0.** 05) **and HIV-infected children** (FA **0.** 25; **95% CI, 0.** 20 **to 0.** **29**

25) (Figure 4.10). Human rhinovirus has previously been shown to be the most prevalent respiratory viral pathogen detected, using molecular techniques, in children hospitalised with LRTI at CHBAH [539]. Human rhinovirus C has been independently associated with lower respiratory illness

in children<3 years of age in the United 883

Kingdom [557]. While

human rhinovirus group C was associated with case status in 8

PERCH, this group tended to occur in older children presenting with wheeze [558]. Cases enrolled into PERCH in whom human rhinovirus group A was detected were more likely than cases with human rhinovirus group C to have radiologically-confirmed pneumonia, and those with human rhinovirus group A mono-infection were more likely to have prolonged hospitalisation (>3 days) and had a 6-fold (95% CI, 1.70 to 19.93; P=0.005) higher adjusted odds of in-hospital mortality [558]. 9.2.4Viral-viral and Viral-bacterial Co-infections The molecular techniques implemented in PERCH gave rise to a situation in which almost every case and control was shown to have evidence of infection with more than one potential pathogen (data not shown), and yet the conditional logistic regression models utilised to derive an FA of pathogen association with case status (at a population level: Tables 4.1 through 4.4) purposefully controlled for all other pathogens when interrogating the association of each pathogen with case status. Hence, the analyses presented in this thesis have not interrogated potential pathogen-pathogen interactions associated with case status in the South African PERCH cohort. A 2018 review and modeling study has highlighted the viral-bacterial and viral-viral interactions that have been shown to occur

in the context of infection with influenza virus 116

[559]. Influenza has been shown to facilitate bacterial co-infection and pneumonia, especially with Group A β-haemolytic streptococcus (GAS), H. influenzae, Mtb, Neisseria meningitidis, pneumococcus and S. aureus, in animal, in vitro and human studies [559] and has recently been shown, using a vaccine-probe approach, to facilitate infection with B. pertussis [560]. On the other hand, current influenza infection tends to protect against co-infection

with other respiratory viruses (including other influenza viruses, human 979

rhinovirus, the parainfluenza viruses and RSV) likely through competition for host cells and substrate, although when they do occur, influenza-respiratory viral co-infections tend to be of greater clinical severity [559]. In secondary analysis of the Soweto PCV9 data, Madhi and Klugman [561]

demonstrated that receipt of PCV9 was associated with a 31% (95% CI, 116

15% to 43%) reduction in hospitalisation for virus-associated pneumonia. Significant associations were inferred between pneumococcus and

influenza A, and pneumococcus and parainfluenza viruses 1-3 903

in the cohort as a whole, between pneumococcus and RSV in HIV-uninfected children, and between pneumococcus and influenza A in HIV-infected children [561]. This analyses indicated that pneumococcus was frequently associated with viral pneumonia requiring hospitalisation in the pre-PCV era. Human rhinovirus may facilitate pneumococcal pneumonia through enhancing pneumococcal adherence to the respiratory epithelium – yet another indicator of pneumococcal-viral interactions that may have clinical relevance [562]. Facilitative viral-viral co-infections have been observed with human rhinovirus and adenovirus [249, 313, 532], human rhinovirus and RSV [313, 563], RSV and adenovirus [313], RSV and human bocavirus [563], human rhinovirus and human bocavirus [563], enterovirus and adenovirus [313] and enterovirus with human coronavirus and parainfluenza virus type 4 [564]. Conversely, the combination of human rhinovirus and enterovirus or human rhinovirus and parainfluenza virus type 3 appear to be uncommon, indicating a degree of competition between these agents [564]. In the Drakenstein study, no pattern of co-occurrence of respiratory pathogens was found to be significantly indicative of case status [250]. The South African PERCH database will prove to be a rich source from which to explore pathogen-pathogen interactions and their association with disease severity, including fatal outcomes, and will assist in generating future research from the site which will explore interactive patterns of infection further. 9.2.5Is There a Place for Shortening or Withdrawing Antibiotic Therapy

in Children Hospitalised with WHO-defined Severe or Very Severe Pneumonia? 25

In the era before HibCV and PCV were available, childhood pneumonia precipitating hospitalisa- tion was frequently caused by mixed bacterial and viral infection, which prompted the WHO to recommend the

use of antibiotics for the treatment of pneumonia in children [565]. In the 704

PCV13 era, there has been a significant reduction of hospitalised paediatric radiologically-confirmed pneumonia associated with high-level (>100 mg/L) CRP on serum testing (levels highly asso- ciated with confirmed pneumococcal disease [566]), suggesting that pneumococcus has lost its primacy as a cause of disease in low-HIV prevalence settings [567]. Now that HibCV and PCV are widely available, it may be possible to shorten, or even withdraw, antibiotic therapy in selected groups of (HIV-uninfected) children presenting with WHO-defined pneumonia [568–570]. In 1998, results of a pivotal trial of short-course (5-day) oral antibiotic therapy compared to co-trimoxazole as outpatient therapy for paediatric

non-severe and severe pneumonia in Pakistan were published in The 471

Lancet [571]. Oral amoxicillin was shown to be superior to

co-trimoxazole in treatment of children with severe pneumonia, 471

including those with bacteraemia, and

predictors of treatment failure in children with severe 950

disease included radiologically-confirmed disease and co-trimoxazole therapy (P<0.01 for each), but not young age (<1 year; P=0.056) [571]. This trial held importance for settings of low HIV prevalence, in which P. jirovecii would not be an important aetiologic agent

(as a cause of opportunistic infection in HIV- exposed or -infected children). 822

A multi-site randomised controlled trial [572], and follow-on trials conducted in South-East Asia, indicate that a 3- to 5-day course of high-dose amoxicillin may be sufficient to manage severe paediatric CAP in carefully selected patients [565, 573]. Short-course oral amoxicillin

is not appropriate for HIV-infected children with severe 825

pneumonia, especially if <12 months of age in whom P. jirovecii contributes to a substantial burden of disease [186, 572, 574]. Antibiotic therapy for bronchiolitis

in children <2 years of age has been 564

established, through meta-analysis, not to be warranted [575] except in children in whom bacterial co-infection is suspected [576, 577]. CRP As a Guide to Pneumonia Aetiology Attribution In PERCH, CRP was found to be a useful discriminatory test to distinguish between cases with bacteriologically-confirmed pneumonia (i.e. bacteraemic, or LA/ PF culture or FTDResp-33 positive for bacterial organisms) and cases with RSV-associated pneumonia (RSV FTDResp-33 positive and not bacteriologically-confirmed) [485].

A cut-off value of CRP ≥40 mg/L had 931

previously been shown to increase vaccine efficacy estimates of PCV9 in preventing disease attributed to pneumococcus more accurately than did chest radiographic findings in HIV- uninfected and -infected children [578]. Although CRP has been shown to discriminate reliably between cases of bacteraemic and viral pneumonia at CHBAH, overlapping results between groups may lead to difficulties in establishing a reliable cut-off value which could be used to guide commencement or withdrawal of antibiotic therapy [579]. Point-of-care CRP testing has been shown to significantly reduce antibiotic prescribing in children and adults with non-severe respiratory infections in Vietnam [580], and adults with upper respiratory tract illness in Ethiopia [581]. In a Belgian study, point-of-care CRP testing, together with assessment of easily-obtainable clinical parameters, permitted stratification of a paediatric cohort (one month to 16 years of age)

into low-, intermediate- and high-risk groups with high 986

negative predictive capacity (99.6%; 95% CI, 99.2% to 99.8%) [582]. CRP was also shown to have better discriminatory value than procalcitonin in distinguishing between children with and without complicated pneumonia in a Swiss study [569]. In a study from Israel, point-of-care CRP testing in an emergency department reliably discriminated between children with bacterial and those with viral pneumonia, especially in those presenting within 96 hours of symptom onset, but did not impact on antibiotic prescribing in the cohort [583]. Few studies have evaluated point-of-care CRP testing in children in Africa [584, 585]. In a study using point-of-care CRP to guide management in neonates with suspected septicaemia, a point-of-care CRP assay exhibited excellent negative predictive value (97% to 99%, depending on timing of the test and the cut-off value used) in discriminating between those with and without bacteraemia [584]. Although point-of-care CRP testing exhibited poor sensitivity and specificity for

Integrated Management of Childhood Illness (IMCI) defined **pneumonia** in a cohort **of** Tanzanian **children** | **78**

with fever in whom malaria had been excluded, the test again exhibited reasonable negative predictive value (87.8%; 95% CI, 82.8% to 91.5%) [585], and may therefore be a useful tool to guide the use of empiric antibiotic therapy in selected febrile patients. Future studies on the utility

of point-of-care testing to guide the **use of** | **895**

antibiotic therapy in children hospitalised with

WHO-defined severe pneumonia in South Africa **would be important to** | **784**

undertake, but would necessarily have to factor in the significant

burden of non **-respiratory virus associated pneumonia in** HIV-infected **children.** | **15**

9.3A Potential Shift in Bacterial Attribution of Paediatric Pneumonia Although antibiotic exposure prior to collection of blood cultures and NP/OP swabs may have impacted to some extent on the yield of pneumococcus from clinical specimens in South African PERCH cases, availability of PCV and its effectiveness in preventing disease caused by vaccine- serotype pneumococci may also have contributed to a reduced burden of pneumococcal disease at the site. The case-control analyses

presented in this thesis highlight **the importance of** non **-type** | **362**

b H. influenzae (FA 0.14; 95% CI, 0.10 to 0.17) and S. aureus (FA 0.09; 95% CI, 0.06 to 0.10) as important contributors to the site-specific ‘aetiology pie’ (Table 4.1) – an important shift away from pneumococcus and Hib as the foremost pathogens in the era before availability of PCV and HibCV. This may represent replacement within an ecological niche (the nasopharynx) that was previously filled by pneumococcus and Hib. In two often-cited articles published in 2004, Bogaert et al [586] and Regev-Yochay et al [587] described an inverse relationship between nasopharyngeal vaccine-type pneumococcal and S. aureus colonisation in children in the Netherlands and Israel, respectively, in the era before PCV immunisation. Whilst pneumococcus, H. influenzae and M. catarrhalis are known to facilitate nasopharyngeal colonisation in a synergistic manner, either though bacterial-bacterial interactions or host-environmental factors [588], competitive interactions have been observed between H. influenzae and S. aureus [589]. In the PERCH South African cohort, S. aureus were significantly associated with case-status with radiologically-confirmed pneumonia in all children, HEU children (FA 0.09;

95% CI, 0. 02 **to 0.** 12) **and HIV-** unexposed **children** (FA **0.** 06; **95% CI, 0.** 03 **to 0.** | **29**

08) (Tables 4.1 through 4.3). In HIV-infected children, S. aureus was associated with case status only in the marginal logistic regression analysis (aOR 4.39; 95% CI, 1.70 to 11.33), but when controlling for all other pathogens, this association was no longer discernable (aOR 2.74; 95% CI, 0.72 to 10.45) (Table 4.4). Staphylococcus aureus also featured prominently in the ‘aetiology pies’ of children dying of pneumonia in the South African PERCH cohort (Figure 4.5), particularly in those <12 months of age (Figure 4.7) and those with very severe pneumonia (Figure 4.10). The empiric antibiotic regimens recommended by the WHO in pneumonia case management target pneumococcus (including penicillin non-susceptible isolates) and Gram-negative organisms (particularly Haemophilus spp. and Enterobacteriaceae), but do not specifically target S. aureus. Staphylococcus aureus was isolated on blood culture in six South African PERCH cases (five HIV-uninfected and one HIV-infected (Tables 3.2 and 3.4)), being the most frequently isolated invasive pathogen in the cohort. There may be scope to broaden antibiotic cover in infants presenting with very

severe pneumonia so as to treat S. aureus, should the clinical picture warrant it. South African paediatric CAP guidelines recommend the empiric use of cloxacillin in children presenting with pneumonia in whom there is a clinical suspicion of disease caused by S. aureus (pneumatocoele or empyema on chest radiograph, or non-resolution of pyrexia within 48 hours of commencing amoxicillin) [590]. 9.3.1Bordetella pertussis as a Threat to Infants Although B. pertussis was associated with radiologically-confirmed pneumonia in the entire South African PERCH cohort (FA 0.02; 95% CI, 0.01 to 0.02), clustering specifically amongst HIV-unexposed children (FA 0.02; 95% CI, 0.01 to 0.02) (Tables 4.1 and 4.3) it was associated with death in a substantial number of cases (FA 0.08; 95% CI, 0.04 to 0.08) (see page 124 and Figure 4.5). Deaths due to B. pertussis were concentrated amongst children <12

months of age (FA **0.** 09; **95% CI, 0.** 04 **to 0.** **100**

10) (see page 137 and Figure 4.7). The epidemiology of B. pertussis in the PERCH cohort has been described [591], again highlighting the important contribution to pneumonia-associated mortality in infants, despite the relatively small role played by this pathogen in the overall child CAP burden. Risk factors for B. pertussis pneumonia in PERCH included young age (too young for immunisation: aOR 16.06, P<0.0001), malnutrition (aOR 6.30; P<0.0001), being unvaccinated (aOR 3.69; P=0.005) and (although not statistically significant) being HEU (aOR 2.17; P=0.053) [591]. A similar

(non-significant) trend towards a greater burden **of** pertussis **in** **912**

HEU compared to HIV-unexposed infants was observed in another study conducted in Soweto [592]. A recent study from Gauteng suggests that HIV-exposure status is not a risk factor of pertussis (disease confirmed by PCR in 5.5% (12/218) HEU and 6.3% (43/678) children; P=0.65), however [593]. Clustering of pertussis-associated

morbidity and mortality in young **infants too young to** have been **fully** **795**

immunised has been well described in the literature [593–596], which has prompted antenatal pertussis vaccination programmes in many developed countries [597–600]. Pertussis incidence rates (per 100 000 infants) in PERCH (90.2; 95% CI, 86.0 to 94.5) (Table 5.2) were lower than those described by Soofie et al [592] (220; 95% CI, 160 to 280). This likely represents the wider field of clinical presentation included in that study (inclusive of LRTI and neonatal sepsis episodes) than was enrolled in PERCH. There is currently no National directive on administration of pertussis vaccination to expectant mothers in the antenatal period in South Africa. Adoption of such a programme, as with a National programme to encourage the routine use of influenza virus vaccination during pregnancy [601], may impact favourably on the burden of pneumonia hospitalisation and mortality in infants. Planning for wide-spread use of these vaccines in LMICs would require careful cost-benefit analyses, and vaccine preparations optimised for effectiveness in routine clinical settings [601]. 9.4Three Important Opportunistic Pathogens This Section highlights

the burden of pneumonia **attributable to** CMV, Mtb **and** P. jirovecii **in** the **South** **559**

African PERCH cohort. 9.4.1CMV

as a Cause of Pneumonia in South African **338**

Children Investigators have questioned the role of CMV in pneumonia aetiology, as detection of the organism in respiratory fluids or blood may represent periodic re-activation of infection and not necessarily disease [192, 518, 602–604], and when detected on post-mortem lung biopsy is frequently identified in conjunction with other agents, especially P. jirovecii [603, 605], which may be construed to contribute more to the pneumonic process than does CMV. An illustration of this from the adult literature, is that in a study of AIDS patients (median age 42 years) in the United States, CMV-associated end-organ disease was seen in 14 (20.6%) of 68 subjects with CMV viraemia and none of the deaths (19 of which occurred in participants with CMV viraemia) was considered to be related to CMV end-organ disease [606]. The series of studies presented in this thesis support the notion that CMV is not only a bystander organism detected in immunocompromised children, but acts

as an important pneumonia **pathogen** in **children under-5 years of age** **in** **421**

the South African context. In PERCH and PLANS at the South African site, CMV as detected on NP/OP swabs in cut-off levels greater than that which best distinguished between cases and controls featured

prominently in association with under-5 radiologically-confirmed pneumonia in HIV-infected and HEU children after adjusting for age (in months), season and all other pathogens (FA 0.35

(95% CI, 0. 17 **to** 0.42) **and 0.** 16 **(95% CI, 0.04 to 0.** 23), **respectively)** (Tables **4.** 2 and **4.** 587

4), as well as in

children in whom post-mortem lung biopsies were indicative **of** 364

fatal CMV pneumonia (Table 7.1). CMV detected on NP/OP swabs was also significantly associated with in-hospital

death in HIV-infected and HEU **children**<12 **months of age** 489

(FA 0.58

(95% CI, 0. 24 **to 0.** 60) **and 0.** 57 **(95% CI, 0.** 18 **to 0.** 57), **respectively)** (see page 139 **and** 428

Figure 4.7). The only organism, as detected on NP/OP swab PCR, that was associated with radiologically-confirmed

pneumonia in HIV-infected children ≥12 months **of age, was** 398

CMV (FA 0.25; 95% CI, 0.08 to 0.26) (Figure 4.8). Additionally, in analysis of a highly select group of radiologically-confirmed pneumonia cases – those with 'severe composite' disease and high-density CMV carriage in the NP/OP space (Section 8.3) – CMV detected on PCR of whole blood was significantly associated with case status in

HIV-unexposed, HEU and HIV-infected children in 185

the South African PERCH cohort, and at feasibly increasing incremental fractions of association between the groups (FA 0.21

(95% CI, 0. 10 **to 0.** 26), **0.** 40 **(95% CI, 0.** 11 **to 0.** 46) **and 0.** 55 **(95% CI, 0.** 39 **to 0.** 239

59) in HIV-unexposed, HEU and HIV-infected children, respectively) (see pages 195 and 198). In each of these analyses, cases with 'severe composite' disease and high-density CMV NP/OP carriage were significantly younger than controls (Tables 8.2 through 8.4). Blood CMV PCR held promise in terms of tempering the possibly inflated pneumonia attributions due to CMV estimated through PCR of upper airways secretions in the PERCH South African cohort. For instance, in

HIV-infected children with radiologically-confirmed **pneumonia, the** FA **of CMV** 137

(as detected in NP/OP FTDResp-33) was 0.35 (95% CI, 0.17 to 0.42) (Table 4.4) whereas the FA of CMV (as detected in whole blood) was 0.25 (95% CI, 0.00 to 0.34) (Table 8.1). HIV-infected

infants have been demonstrated **to have significantly higher rates of** 813

congenitally- acquired CMV infection, as evidenced by positive PCR testing of stored urine specimens collected within 48 hours of birth, than do HEU infants [607]. Furthermore, HIV-infected mothers have been demonstrated to be effective transmitters of CMV infection through breastfeeding, despite increased access to ART [608]. Infants in Southern Africa tend to manifest a biphasic pattern of CMV viraemia prevalence, reflecting early primary infection

637

(at 1 to 3 months of age) and reactivation disease (at 18 to 24 months of age)

which is more pronounced in HIV-infected children [609]. A study from Durban which interrogated the outcomes of children ventilated in an ICU setting highlighted poor clinical outcomes in children with CMV pneumonitis treated with ganciclovir compared to those with evidence of CMV infection not treated with ganciclovir (mortality 10/38 (26.3%) versus 0/27 (0.0%), respectively; P<0.05) [518]. Poor survival in the former group was likely associated with greater disease severity as evidenced by significantly higher rates of acute respiratory distress syndrome, septic shock, HIV/AIDS and requirement for high frequency oscillatory ventilation in the group that received ganciclovir. Adenoviral and Candida spp. co-infection

was also significantly more prevalent in children treated with 894

ganciclovir [518]. Ganciclovir therapy was administered to children with positive CMV results, predominantly reticular changes on chest radiograph and lack of clinical improvement on broad-spectrum therapy for bacterial or P. jirovecii pneumonia; hence the study design was not appropriate

to evaluate the utility of ganciclovir in children with evidence of CMV pneumonia. 120

The authors conceded that an RCT of ganciclovir versus placebo

in the treatment of children with CMV-associated pneumonia would be 963

the only means by which to optimally evaluate the use of ganciclovir in children with severe pneumonia [518].

In a prospective study of ventilated HIV-infected and -exposed children 821

from Pretoria, the highest CFRs were seen in children in whom CMV was detected on whole blood PCR with and without P. jirovecii co-infection (58.3% (7/12) and 36.4% (8/22), respectively) whilst none of the nine children with P. jirovecii pneumonia without concomitant CMV infection died [217]. All children received empiric co-trimoxazole, ampicillin and amikacin, as well as ganciclovir until CMV whole blood levels were <10 000 copies/mL. The CFR amongst HIV-infected children was 32.1% (17/53) in HIV-infected children [217]. Goussard

et al [204] described the outcomes of 25 HIV-infected children 137

ventilated for suspected P. jirovecii pneumonia with poor clinical response to co-trimoxazole therapy, in which there was an inordinately high (88.0%) in-hospital mortality rate. Histology revealed the presence of CMV in the majority (88.2%; 15/17) of those from whom lung biopsies were obtained [204]. The use of empiric ganciclovir therapy has been adopted in many centres treating HIV-infected children ventilated for severe pneumonia in South African hospitals [204, 211], and evidence for this intervention has been strengthened by an observational study from Vietnam which demonstrated favourable side effect profiles and low case-fatality (2.3%; 1/43) in young non-immunocompromised infants ventilated for CMV-associated pneumonia [610]. Case fatality ratios amongst children with HIV-infection ventilated in South African ICUs have declined substantially in response to clinical guidelines advocating the use

of co-trimoxazole and ART for the treatment of P. jirovecii pneumonia 805

and HIV disease. In the era before such interventions were widely implemented, CFRs were in the region of 88% to 100% [135, 146]. Current CFRs of under 30% as presented by Kitchin et al [217] and Jeena et al [518] may reflect improved empiric therapy offered to HIV-infected children with respiratory failure, which includes the use of co-trimoxazole, ganciclovir and ART in addition to broad spectrum antibiotic cover for bacterial pneumonia. Hsiao et al [226] formulated a cut-off density of CMV DNAemia of 4.1 log10 copies/mL on whole blood as best distinguishing between paediatric cases of CMV pneumonia and controls. This, 4.1 log10 copies/mL cut-off density of CMV on whole blood is considerably higher than the cut-off densities (ranging from 2.53 to 3.34 log10 copies/mL) which best distinguished between cases with radiologically-confirmed pneumonia and controls in the PERCH South African cohort (see Table G.1). Discrepancies in cut-off densities probably relate to differences in study design and choice of control groups between studies, as well as the well-described short-fall in drawing parallels between studies in which different laboratories using different assays produce unstandardised CMV viraemia levels [514]. The WHO reference standard for universal comparison of CMV viral load results [514, 515] was not applied to any of the assays used in PERCH, or in Hsiao's Cape Town-based study. It is regrettable that such a standardisation step was not incorporated into the PERCH CMV NP/OP and whole blood PCR analyses. At best, the CMV whole blood

sub-study at the South Africa site can only estimate the burden of pneumonia associated with CMV in a sub-set of children with clinical features supportive of a diagnosis of CMV pneumonia. The sub-study cannot be prescriptive of a diagnostic cut-off level which best distinguishes CMV- disease from non-CMV pneumonia, because of lack of a standardisation procedure for CMV viral load in NP/OP swabs and whole blood. Vaccines targeting CMV are under development, with the driving force behind their development being a need to reduce the burden of congenital CMV disease, or primary CMV disease in transplant recipients [611, 612]. Modelling studies suggest that the most effective vaccine strategy would be to target young children, adolescents and

women of child-bearing age [613, 614]. **The** importance **of** CMV being **associated** **921**

with CAP in young, and particularly

HIV-infected and -exposed **children in our setting,** suggests that perhaps **the** major benefit **of** **241**

implementation of vaccination programmes targeting CMV for

prevention of transmission of the virus **from mothers to their infants** **374**

may not be solely in reducing congenital CMV infection, but rather in the reduction of the burden of early infantile CMV-associated pneumonia, with its attendant

morbidity and mortality in the **sub-Saharan African** context. 9 **.4.** **288**

2Is Tuberculosis Cause or Risk Factor for Acute Pneumonia? Modelling studies indicate that 327 237 (IQR, 205 206 to 494 575)

children <5 years of age developed TB disease **in** 2010 in **the** 22 **high-** **403**

burdened TB countries, 77% (IQR, 64% to 87%) of which were PTB cases [615], and that 191 000 (95% Uncertainty Interval, 132 000 to 257 000) under-5 TB deaths occurred in 2015 [616]. Mycobacterium tuberculosis

is one of the top 10 causes of childhood **761**

death globally, with >96% of all children dying of TB not accessing anti-tuberculosis therapy [616]. In the pre-chemotherapeutic era, the mortality rate associated with TB in

children <5 years of age was 43.6% (95% CI, **7**

36.8% to 50.6%) which has improved to a CFR of 2.0% (95% CI, 0.5% to 7.4%) in pooled estimates of studies conducted subsequent to 1980 [617]; hence, high modelled TB-associated mortality rates [615, 616] are highly suggestive of suboptimal treatment coverage in young children with TB. In South Africa, 7% to 12% of notified TB

cases occurred in children<15 **years of age** **154**

in 2012 through 2015 [618–621]. The burden on childhood TB is indicative of an unchecked epidemic of Mtb transmission in South Africa which largely reflects transmission of infection from household contacts to young children in this high-burdened setting, although roughly 25% of transmission to young children occurs through contact with adults not resident in the household [622]. In a study conducted in Soweto in 2010 through 2012, when using newly-diagnosed PTB in children <7 years of age as a sentinel event and actively screening the households of those children, 4.3% (23/541) of caregivers were found to have microbiologically-confirmed TB which was often coupled with undiagnosed HIV infection [623]. There are no National coverage data of isoniazid preventive therapy (IPT) in South Africa, but various studies indicate that a minority (1.3% to 35.7%) of children eligible to receive IPT access treatment [624–628], with poor adherence to therapy in those that do [629]. South African pneumonia aetiology

studies conducted in the pre- ART, pre **-PCV era** demonstrated **that** **116**

Mtb, diagnosed by means of GA in most instances, was associated with 8% to 15% of acute pneumonia cases

among children <5 years of age hospitalised in **public** sector **hospitals** **858**

[158, 192, 630]. As the sensitivity of GAs for Mtb culture is only in the region of 20% to 40% [255, 631], it is likely that the burden of disease attributed to Mtb was underestimated in those studies. A large proportion (43% to 85%) of South African paediatric culture-confirmed Mtb cases present with cough duration <2 weeks [192, 632, 633], which differs from the classical opinion that PTB in children represents a subacute or chronic disease process [634]. A

post hoc analysis of the Soweto **PCV9 trial** cohort demonstrated **that** **535**

there was a 43% (95% CI, 9.7% to 65.1%) reduction in culture-confirmed PTB amongst children <5 years of age that had received PCV9 compared to placebo recipients [633]. As there is no biologically plausible reason to explain protection from Mtb through administration of PCV, the findings of that study suggested that culture-confirmed PTB is commonly associated with an acute episode of pneumococcal pneumonia [633]. In the era post

-introduction of ART into the South African public health sector, **721**

there has been

a significant reduction in incidence of culture-confirmed PTB **in** Sowetan **children** **16**

(3

months to<15 **years of age),** from 69.8 **per** 100 **000 children** **557**

in 2005 to 25.8 per 100 000 children in 2009 (a 63.1% (95% CI, 52.8% to 71.1%) reduction) (pre-PCV era) with a further (non-significant) reduction in incidence to 16.3 per 100 000 children in 2012 (post-introduction of PCV) [635, 636]. Furthermore, there has likely been a significant reduction in the force of Mtb infection at community-level as a direct result of improved access onto ART amongst HIV-infected adults, in whom significant reductions in the incidence of culture-confirmed Mtb have been demonstrated throughout South Africa [637]. These studies suggest that ART, through improving the immunological response in HIV-infected patients (paediatric and adult)

has had a major **impact in reducing the burden of** **56**

Mtb infection, and culture-confirmed PTB in South Africa. An interesting sequence of influenza-pneumococcal-Mtb seasonality was described in a secondary analysis of the PTB time-series paper of childhood culture-confirmed PTB in Soweto mentioned above [635]; whereas influenza seasonal peaks occurred in May through July, hospitalisation for invasive pneumococcal disease peaked in August through October, followed by hospitalisations for culture-confirmed PTB (in August through November) [638]. Interactions between influenza and Mtb in patients participating in the SARI Study have been also been published [639], and highlight that patients with influenza-Mtb co-infection, and symptom duration ≥7 days, had a 6.1

-fold (95% CI, 1. 6 **to** 23.4) **greater** adjusted relative **risk of** **29**

dying compared to patients with culture-confirmed Mtb without concomitant influenza. Difficulties in arriving at a definite

diagnosis of TB in children are **a major** contributor **to the** under-representation **of** culture-confirmed **disease,** **489**

particularly

in the under-5 age group. At the PERCH **South** African site, **the** **842**

majority (81.5%; 119/146) of children assigned a discharge diagnosis of 'TB' by ward clinicians did not have culture confirmation of their condition (see Section 6.1.3). This clearly reflects the poor sensitivity of the standard armamentarium of TB diagnostics available to clinicians, and possibly a reluctance amongst clinicians to miss a diagnosis of TB with a clinical bias rather to err on the side of empiric anti-tuberculosis treatment. Positive Mantoux responses, malnutrition and increasing age were significantly associated with a ward clinician decision to initiated anti-tuberculosis therapy in children under their care (Table H.3). Importantly, the prevalence of culture-confirmed Mtb infection in the South African PERCH cohort (2.9%; 27/902) was substantially lower than estimates from

studies conducted in the pre- ART **era. The** yield **of** 54

IS and GA were equivalent in PERCH, which differed from the findings of a study which interrogated the utility of IS compared to GAs

in HIV-infected and -uninfected children with suspected PTB **in** 10

Cape Town [255]. In the study by Zar et al [255], the yield of Mtb from one IS was equivalent to that of three GAs. Children in the Cape Town-based study were selected for enrolment if they presented with chronic cough (>28 days), and at least one of a household TB contact, failure-to-thrive, a positive Mantoux response, or a suggestive chest radiograph [255], and therefore the cohort was enriched for children likely to have an underlying diagnosis of PTB. In PERCH, no such criteria were required for sampling of cases using GAs and ISs for investigation of PTB, which mirrors routine practice at CHBAH where there is

a high index of suspicion of PTB **in** young **children** hospitalised **with** 39

CAP. A combination of two GAs and two ISs arrived at the best yield of culture-confirmed Mtb (4.0%; 12/300) in the PERCH cohort (see Figure 6.2). Mantoux test positivity was high in cases (14.7%; 58/920) and controls (17.6%; 10/56) in PERCH South African participants, and case Mantoux positivity was greater in the convalescent period after recovery from the hospitalised pneumonia episode (36.8%; 14/38) (Section 6.3). After controlling for age (in months), cases had a 2.9-fold (95% CI, 1.09 to 7.84) higher adjusted odds of being Mantoux-test positive after recovery from the pneumonia which precipitated their hospitalisation in PERCH than controls. While interference with case Mantoux positivity through boosting may have played a role in case convalescent Mantoux test positivity [640], the phenomenon of enhanced tuberculin skin test reactivity after recovery from a preceding pneumonia episode is intriguing, possibly pointing to a role of latent tuberculosis being a risk factor for childhood CAP requiring hospitalisation. Future studies of childhood pneumonia should evaluate Mantoux test responsiveness at two time points – during the acute illness and in the convalescent period – in order to evaluate whether an intercurrent pneumonia episode dampens a child's response to PPD. Of 915 infant-mother pairs followed longitudinally in the Drakenstein Study, 45 (4.9%) were diagnosed with TB disease and 18 (2.0%) had culture-confirmed TB [628]. There were high rates of tuberculin skin test conversion (16%; 147/915), clinically-diagnosed TB (2 900 per 100 000 children) and culture-confirmed TB (700

per 100 000 children) **in children under-** 5 **years of age in** 710

the Drakenstein Study [628, 641]. The only factor independently associated with microbiologically-confirmed TB in Drakenstein was LRTI (aOR 9.06; 95% CI, 2.08 to 39.42, P=0.0033) with 65% of LRTIs occurring two weeks after the culture-confirmed TB episode [628]. Whether the interactions between Mtb, and bacterial and viral organisms causative of CAP hinge on perturbations in the innate and adaptive immune caused by latent Mtb infection, which may impair the ability to contain colonising bacterial populations in the nasopharynx, predisposing to bacterial pneumonia, or an acute viral or bacterial pneumonia leads to 'escape' of latent Mtb infection predisposing to active PTB, is the subject of intensive debate [642]. It would appear, from evidence presented through PERCH at the South African site and Drakenstein, that latent TB

is an important risk factor for childhood CAP, **however.** 9.4.3PJP **in** 478

the South African PERCH cohort The burden of disease associated with P. jirovecii in the South African PERCH cohort was considerable, even in HIV-uninfected children (Table 5.2), and P. jirovecii was associated with in-hospital mortality in HIV-unexposed (FA 0.18; 95% CI, 0.15 to 0.18), HEU (FA 0.25;

95% CI, 0. 13 **to 0.** 25) **and HIV-infected children** (FA **0.** 52; **95% CI, 0.** 46 **to 0.** 29

53) (pages 127 and 133; Figure 4.6). In the pre-ART era, P. jirovecii pneumonia (largely diagnosed using IFA) was shown to be an important aetiologic agent in pneumonia in

HIV-infected children, particularly **in** those **<1 year of age** 5

[134, 153, 162, 643]. Subsequent studies have highlighted the lack of sensitivity of IFA-based diagnostic assays for P. jirovecii, compared to PCR as well as the equivalent yield using PCR on upper respiratory tract rather than lower respiratory tract secretions [240, 644]. Estimates of disease associated with P. jirovecii as presented in Table 5.2 represent a novel aspect of the analyses; in no previous studies have attempts been made to quantify the burden of childhood illness associated with this pathogen in South Africa. Amongst HIV-infected

children under one year of age, the incidence of 386

P. jirovecii -associated pneumonia was 3 635.7 per 100 000 children (95% CI, 3 132.0 to 4 197.4 per 100 000 children) – second only to CMV in terms of incidence rate in this age group (Table 5.2). In HEU infants, the P. jirovecii -associated pneumonia incidence (per 100 000 children) was 381.1 (95% CI, 352.5 to 411.4), similar to the incidence rates of adenovirus-associated (352.4; 95% CI, 326.0 to 380.5) and human bocavirus-associated pneumonia (325.8; 95% CI, 301.4 to 351.7) (Table 5.2). Similarly, in HIV-unexposed children, the incidence (per 100 000 children) of P. jirovecii -associated pneumonia (113.6; 95% CI, 106.2 to 121.3) was similar to the incidence rates of disease associated with adenovirus (112.0; 95% CI, 104.8 to 119.6) and HMPV (124.8; 95% CI, 116.7 to 133.3) (Table 5.2). Risk factors for P. jirovecii pneumonia in children include HIV-infection or -exposure [643, 645, 646], immunosuppression from immunomodulatory therapy in organ transplant recipients or cancer chemotherapy [647] and malnutrition [648]. Pneumocystis jirovecii pneumonia

has been shown to be associated with pneumonia mortality **in children** 41

<5

years of age (OR 4.79; **95% CI, 2.** 67 **to** 89

8.61) [649]. Chintu et al [650] conducted an RCT

of co-trimoxazole prophylaxis in HIV-infected infants **in Zambia** 538

from March 2001 until its early termination in October 2003, and established the efficacy of co-trimoxazole over placebo in substantially reducing mortality

(Hazard Ratio 0. 57; **95% CI, 0.** 43 **to 0.** 77). **The** 14

WHO published a statement on co-trimoxazole prophylaxis in children in November 2004 [651], recommending that co-trimoxazole should only be discontinued in

HIV-exposed children if **HIV infection has been** confidently **ruled out, and no longer breastfeeding.** 51

These guidelines for co-trimoxazole prophylaxis have not been updated, and have been reiterated in the current WHO consolidated

guidelines for the management of HIV- infected and -exposed **children** 747
[652]. Implicit **in the**

WHO co-trimoxazole prophylaxis guidelines, was that HEU children could discontinue prophylaxis in the first year of life if no longer breastfeeding and testing negative by nucleic acid based tests conducted

six weeks after cessation of breast feeding. Alternatively, in HEU **infants** 374

never exposed to breastfeeding, a negative six or 10-week HIV PCR would constitute justification to discontinue co-trimoxazole prophylaxis. In sub-Saharan African settings in which

co-trimoxazole prophylaxis has been shown **to** impact on **survival** of HEU **children,** **865**

this protective effect has been attributed more to prevention of malaria than to prevention of P. jirovecii pneumonia [653–655]. In a Malawian study which evaluated the

use of co-trimoxazole prophylaxis in HEU **children,** **967**

LRTIs and diarrhoeal illness were significantly reduced in those children assigned to the treatment arm of the study compared to placebo recipients (Hazard Ratios

0.64 (95% CI, 0.60 to 0.69) and 0. 59 **(95% CI, 0.** 54 **to 0.** 65), **respectively)** **239**

[656]. An important limitation of the Malawian study was that co-trimoxazole prophylaxis was not randomised, but non-receipt or receipt of the drug was dependent on calendar time (with children enrolled into the study prior to June 2006 assumed not to be co-trimoxazole exposed) [656]. In Botswana – a setting of low malaria endemicity, low maternal-to-child HIV transmission risk and low breastfeeding rates – co-trimoxazole prophylaxis for HEU infants was shown to deliver no survival advantage over placebo at 18 months of age [657], but posed a risk for neutropaenia and carriage of co-trimoxazole resistant bowel flora [657, 658].

Co-trimoxazole prophylaxis has **also** been **associated with** high carriage **rates of** **538**

resistant bacteria in the upper respiratory tract in HIV-infected children [659]. Coutsoudis et al [181] observed significantly reduced LRTI-associated morbidity

in HIV-infected (aOR 0. 18; **95% CI, 0.** **558**

04 to 0.77) but not HEU (aOR 0.52; 95% CI, 0.26 to 1.05) infants receiving

co-trimoxazole prophylaxis **in the pre-ART era** (1995 through 1998) **in** **76**

KwaZulu-Natal. Furthermore, in a study conducted in the era of access to ART (2003 through 2010) no benefit of co-trimoxazole prophylaxis was seen in terms of preventing LRTI in HEU infants attending an urban clinic in Durban (IRR 0.71;

95% CI, 0. 39 **to 1.** 26), although **there was a** non-significant **increased risk of** diarrhoea associated **with** **59**

co-trimoxazole use for >60 days (IRR 1.38; 95% CI, 0.98 to 1.94) [660]. An RCT of co-trimoxazole in South African HEU infants is underway at the time of writing this thesis [661]. Findings from the PERCH South African site, which suggest that a considerable burden of P. jirovecii associated pneumonia arises in HEU children, may have bearing in terms of strength- ening the argument

for the use of co-trimoxazole prophylaxis in **906**

HEU infants. 9.5What Does PLANS Tell Us? A review of nine sub-Saharan African childhood post-mortem studies indicated that bacterial pneumonia was the most important histopathologic entity occurring in children dying of pneu- monia (47.0%; 391/832), followed by P. jirovecii (17.9%; 149/832) and CMV (17.4%; 145/832) pneumonia [605]. Tuberculosis was identified on post-mortem in 8.5% (71/862) of the childhood cases reviewed, and was significantly more prevalent

in HIV-uninfected children compared to those that were **HIV-infected** **345**

(11.9% versus 7.3%; P=0.034) [605]. Through PLANS, it is evident that CMV (34.5%; 10/29), P. jirovecii (34.5%; 10/29) and Klebsiella spp. (17.2%; 5/29) were the organisms most commonly associated with fatal pneumonia at the South African PERCH site (see page 186). Pneumocystis jirovecii and CMV on lung biopsy were previously seen to be important pathogens associated with death

pre-ART era [174]. Although the sample size in PLANS was small (n=38 at the South African site), Mtb was not identified in any of the children sampled which may reflect limitations in terms of the minimally-invasive approach being able to detect active tuberculosis, but may also suggest that undiagnosed TB is not an important contributor to pneumonia-related mortality at CHBAH. A large-scale minimally invasive post-mortem study is currently being conducted at CHBAH which will have greater power to define infectious disease associations with childhood mortality in Soweto. 9.6Limitations and Strengths of This Study As with any body of research, the work presented in this thesis has certain strengths and weaknesses, which are described in this Section. 9.6.1Analytic approach Imperfect age-matching of cases to controls Identifying suitable controls and matching them to cases constitute some of the most challenging intricacies of case-control study design, implementation and analysis [662]. Imperfect age-matching may have compromised the South African site analytic outputs to some extent, especially when considering that many of the pathogens tested for appear to be highly age-dependent. However, a decision was taken a priori to match community controls to cases according to age-frequency, so as to alleviate the anticipated difficulties of attaining a strict age-match whilst enriching for an analysis that would best deliver the study objective of describing the aetiology of hospitalised severe or very severe pneumonia [478]. Age-frequency matching permitted a degree of robustness in the dataset, which was anticipated to ameliorate imperfect age matching. Frequentist versus Bayesian approaches to analysis The frequentist approach used in the analyses contained in this thesis were based on comparisons of imperfect proxy measures (NP/OP swabs and whole blood) of what was actually occurring at the site of pathology (the lungs) in the PERCH cases, and did not integrate the disparate test results (including those derived from blood, PF and LA cultures) which were obtained from cases only. In the PERCH Integrated Analysis (PIA), a Bayesian framework was used through which to achieve a very complex but comprehensive evaluation of pneumonia aetiology attribution in PERCH participants [663]. Analytic outcomes in the PERCH overarching aetiology paper, and site-specific papers, give rise to a nominal residual output of pneumonia aetiology assigned to pathogens ‘not otherwise specified’ in the study, as a result of the Bayesian analysis used. For instance, the fraction of pneumonia attributed to pathogens ‘not otherwise specified’ amongst cases with radiologically-confirmed pneumonia is 1.4% (95% Credible Interval, 0.1% to 4.3%) [295], compared to 0.04 (95% CI, -0.05 to 0.28) 1 in the analysis presented herein (see page 134 and Figure 4.5). Some may argue that the tried-and-tested frequentist approach, as employed in the analyses presented herein, ‘make more sense’ than complex Bayesian models used to derive aetiology attributions. The attributable fraction method employed a systematic approach to the comparison

more intuitive to those that were not involved in the research project but who are confronted with the data for the first time. Rigorous commentary regarding the strengths and failings of both approaches will no doubt be entered into once the overarching PERCH aetiology paper becomes available to a wider academic readership. Population-level estimates and not individual-level analysis The attributable fraction method used in the case-control analysis presented here gives rise to estimates of the fraction of pneumonia arising in the cases that would be prevented if the implicated organism was removed from the community (through interventions such as vaccination, for example) [454]. Hence, these are population-level estimates which cannot be translated directly back to individual participants in PERCH at the South African site. It is for this reason that no 1 Note the intentional discrepancy in reporting here: PERCH overarching paper AFs were reported as percentages, whereas the FA presented in this thesis are reported as proportions. Converting the FA to percentages would lead to an AF of 4.0% (95% CI, -5.0% to 28.0%) for the ‘unknown’ pathogens associated with the pneumonia episode. pathogen-specific analyses for organisms tested using the FTDResp-33 PCR on NP/OP swabs – such as those conducted by Madhi et al for HMPV [664] or RSV [187] in the early 2000s – have been presented in this thesis. As stated earlier, the molecular diagnostic approach used in PERCH gave rise to a situation in which almost every participant had more than one potential pathogen identified on FTDResp-33 PCR of NP/OP swabs. Consequently, selecting out specifically which pathogen (or group of pathogens) were implicated in the pneumonia episode would be difficult to undertake using the rudimentary statistical methods employed in the analyses presented here. The PIA is capable of deriving population-level and individual-case ‘aetiology pies’ [295]: further work will be needed to fully describe the overarching PERCH and site-specific patient-level pathogen attributions. 9.6.2Paucity of Data from the Site of Infection The case-control analysis presented herein was based on a comparison of NP/OP swabs between cases and controls, as a convenient (although suboptimal) proxy measure of the environment inside the lung. As controls were asymptomatic for WHO-defined pneumonia, it was assumed that their lung fields were sterile. A subset of cases (n=6) underwent lung aspiration, and this represented the ‘gold standard’ measure of aetiopathogenesis at the site of pathology. Limitations of lung aspiration are its invasiveness (which preclude case-control study designs incorporating the technique), and the fact that it is best suited for pneumonia episodes in which there is peripherally located lobar consolidation which can be accessed by transcutaneous needle aspiration. Although there is emerging evidence that the lung is not a sterile environment in a state of health, and that a lung microbiome exists, which if perturbed may give rise to a situation in which pneumonia pathogenesis can ensue [665–668], in studies in which a ‘gold standard’ sample can be achieved, there would be no need for a control group against which to adjust the results of tests conducted in cases. Future pneumonia aetiology studies in children, as well as post-mortem studies,

should incorporate lung aspiration for routine bacterial culture, mycobacterial culture and molecular diagnostic studies. Ideally, LA sampling should be undertaken prior to administration of antibiotic therapy, so as to optimise the yield of bacterial culture from the specimens. Once competency has been achieved amongst clinicians in order to obtain these samples, adverse event profiles associated with lung aspiration are negligible [264]. Indeed, in PERCH at the South African site, none of the six cases that underwent lung aspiration experienced adverse events related to the procedure. 9.6.3Omission of Molecular Testing for Mtb When the first planning meetings around PERCH were underway, molecular

methods for the rapid diagnosis of Mtb **in** 71

clinical specimens were not widely available. It was only in 2010 that Boehme et al [669] published their seminal paper on rapid diagnosis of Mtb in clinical specimens using

Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), which **has** 756

become standard of care in TB diagnostics worldwide having been endorsed for this use by the WHO in 2011 [670]. Unfortunately, this rapid molecular test was not incorporated into the PERCH diagnostic armamentarium and reliance on conventional mycobacterial culture techniques was resorted to at all PERCH sites. Subsequent research has shown the usefulness

of the Xpert® MTB/RIF assay in the diagnosis of 725

paediatric PTB from IS, nasopharyngeal aspirate and stool specimens [671–673], but with lower sensitivity compared to mycobacterial culture in the clinical setting [674]. Newer, ultra-sensitive assays are now available and show promise to have sensitivity approaching that of mycobacterial culture under research conditions [675]. Using the Xpert® MTB/RIF assay on paediatric stool specimens has the advantage of being a particularly 'humane' specimen, which does not require invasive sampling as GAs and ISs do. A pilot study of Xpert® MTB/RIF testing on stool specimens had a 47% sensitivity compared to IS, but substantially better sensitivity in HIV-infected children (80%; 4/5) compared to those that were HIV-uninfected (33%; 4/12) [673]. Future research should interrogate the utility of stool mycobacterial culture using recently developed decontamination procedures, such as the Chlorhexidine decontamination procedure pioneered by Drancourt et al [676], as well as ultra-sensitive molecular assays. 9.6.4Inferential Analysis of CMV Whole Blood PCR Results CMV whole blood PCR testing was prioritised for children testing positive for CMV on FTDResp- 33 PCR testing of respiratory specimens, under the premise that children negative for CMV on testing of respiratory specimens would be unlikely to have high-level CMV viraemia (Section 8.1). For the case-control analysis, CMV results were considered only in children whose CMV densities exceeded the cut-off density which best distinguished between cases and controls using ROC analysis (Table G.1). We reasoned that children hospitalised

with WHO-defined severe or very severe pneumonia and 18

whose pneumonia aetiologic agent was CMV would have the organism detected in respiratory specimens and possibly blood but would be very unlikely to have CMV viraemia in the absence of evidence of the organism in the respiratory tract. Controls may have had CMV viraemia, but were unlikely to have high-level CMV viraemia above the cut-off which best distinguished cases from controls. Whereas it would have been ideal to have evaluated CMV DNAemia in all participants, regardless of the results of FTDResp-33 CMV testing, there were sufficient grounds to conduct the analysis as presented in this thesis.

In a case-control study of CMV viraemia conducted **in** 968

Cape Town, 24% (67/275) control infants had CMV viraemia, but at consistently lower densities than viral loads detected in children with pneumonia [226]. In Zimbabwean infants surviving beyond six months of age, archived sera taken at six weeks of age indicate high

CMV viraemia prevalence **in HEU and HIV-unexposed infants** 945

(81.4% versus 74.0%, respectively; P=0.14) with higher viral loads in HEU infants (median 2.54 log10 copies/mL versus 2.26 log10 copies/mL in HEU and HIV-unexposed children, respectively; P=0.005) [509]. Similarly, in a Kenyan cohort of HEU and HIV-unexposed infants,

there was a high prevalence of CMV viraemia **in** asymptomatic **children** 339

(81.0% versus 45.0%, respectively; P=0.004) but with equivalent viral loads (median 3.1 log10 IU/mL versus 2.7 log10 IU/mL in HEU and HIV-unexposed children, respectively; P=0.161) [510]. By interrogating only a subset of the cohort for CMV viraemia we have likely achieved a conservative estimate of the utility of CMV whole blood PCR testing in children hospitalised with pneumonia in high-burdened settings of HIV in sub-Saharan Africa. 9.6.5Difficulties with Klebsiella pneumoniae Klebsiella spp., identified chiefly through blood and sputum culture, have been implicated as a cause of CAP in 0.3% to 26.7% of adults hospitalised with pneumonia [677–689], and have recently been associated with childhood pneumonia in molecular studies [690]. Furthermore, in review of sub-Saharan African paediatric pneumonia aetiology studies, Klebsiella spp. have been identified in culture of positive blood (3.5%; 74/2 116), sputum (22.6%; 89/393) and LA (7.8%; 29/370) cultures, clearly indicating the importance of these bacteria in childhood pneumonia pathogenesis (see Figure 1.6). In the Drakenstein and PERCH studies, it was decided to exclude Klebsiella spp. from the case-control analysis, over concerns raised regarding the FTDResp-33 assay's specificity for the target pathogen [250, 295]. The FTDResp-33 target for Klebsiella spp. is the khe haemolysin gene, which is considered to be specific to the K. pneumoniae [691], but which also detects K. variicola which is not an important human pathogen [692]. It is unfortunate, given the documented contribution of K. pneumoniae in the aetio-pathogenesis of childhood pneumonia, that this potential pneumonia pathogen was omitted from NP/OP FTDResp-33 PCR analysis in PERCH. 9.6.6Study Strengths PERCH was rigorously standardised, comprehensive in terms of the specimens tested, and state-of-the-art in terms of the molecular diagnostic methods used. These characteristics served to achieve an all-site, and individual-site dataset that is robust and highly representative of the pneumonia case load that presented at each study site during the enrolment period. Being a cross-sectional study, it was able to sample a large

cohort of HIV-infected, HEU **and HIV-** unexposed **children** at **the** South **African** **518**

site. This is in contrast to the longitudinal study design of the Drakenstein study in which few HIV-infected children were enrolled for analysis [250]. The case-control aspect of PERCH permitted adjustment of case NP/OP pathogen prevalence against a sample of healthy controls, which has the potential of achieving more accurate estimates of pathogen-specific incidence rates that would be made by using case-only pathogen prevalence [478, 693]. 10 Conclusions and Recommendations The series of

studies presented in this thesis contribute to a more robust **understanding of** **153**

childhood (under-5) pneumonia aetiology and the burden of disease occurring in Soweto, specifically in the 24- month period in late 2011 through late 2013 in which it was conducted. Of tremendous importance is that the study appraised pneumonia aetiology in the context of a rigorously standardised case-control methodology which used state-of-the art molecular diagnostic techniques to evaluate the potential pathogen associations in an era of established access to bacterial conjugate vaccines, PMTCT and ART. The study had power to evaluate aetiologic associations using a validated frequentist analytic approach for the attribution of disease aetiology within the context of matched case-controls studies not only in the cohort as a whole, but also in three important groups of interest: HEU, HIV-unexposed and HIV-infected children. 10.1Conclusions 10.1.1Key Pneumonia Pathogens Pathogens associated with radiologically-confirmed pneumonia included RSV, adenovirus, parain- fluenza virus type 3 and human rhinovirus, non-type b H. influenzae, S. aureus and P. jirovecii in the combined cohort (Table 4.1), with the respiratory viral pathogens accounting for 60% of the pneumonia episodes (Figure 4.6). Pathogen profiles in HEU and HIV-unexposed children with radiologically-confirmed pneumonia varied substantially (compare Tables 4.2 and 4.3), with a greater proportion of pneumonia episodes in HEU cases being associated with the opportunistic pathogens CMV and P. jirovecii (Figures 4.5 and 4.6). An important aspect of the analysis was that of pathogen associations with radiologically-confirmed pneumonia in HIV-infected children, stratified as to whether they had accessed ART or not prior to enrollment into PERCH (Section 4.2.4). There was sufficient power in the comparisons between case and control groups that had not accessed ART, as well as cases and controls that had accessed ART prior to participation in the study to derive statistically meaningful outcomes in the attributable fraction analysis. Unsur- prisingly, P. jirovecii was associated with case-status in ART-na¨ıve children whereas RSV was the pathogen associated with case-status in the group that had accessed ART prior to enrollment. This 237 reinforces the evidence of the transformative effect that ART has in terms of achieving relative immune competence in HIV-infected children. 10.1.2Pneumonia Incidence Rates Pneumonia incidence rates (per 100 000

children between the ages of one and 59 months **of age)** **249**

were high overall (1 755.0; 95% CI, 1 701.8 to 1 809.5), and decreased with increasing age (Table 5.1), but incidence rates (overall and pathogen-specific) were generally lower than those described in other studies conducted at the study facility [159, 187, 228, 363] most likely as a result of the restricted case-definition

(WHO-defined severe and **very severe pneumonia)** compared **to** **195**

those used in other studies (in which 'LRTI' or 'SARI' were the groups of interest sampled). Nevertheless, significantly higher relative risk of disease was seen

in HIV-infected compared to **HIV-uninfected children** and HEU **compared to HIV-** unexposed **children** 740

(Tables 5.1 and 5.2) as has been appreciated in other studies [363]. A novel aspect of this work is the estimates of burden of pneumonia associated with P. jirovecii which was particularly concentrated in the one to 11 month age group (not only confined to HIV-infected children): in

HEU and HIV-unexposed children in 391

this age group, the incidence of P. jirovecii -associated radiologically- confirmed pneumonia was similar to the pneumonia burden associated with adenovirus and human bocavirus, and adenovirus and HMPV, respectively. This finding may impact on clinical

guidelines for co-trimoxazole prophylaxis in HEU infants. **The** results **of** 897

an RCT of co-trimoxazole prophylaxis versus placebo in HEU currently underway in KwaZulu-Natal are eagerly awaited to resolve this issue [661]. 10.1.3Mtb in PERCH South African Participants Mycobacterium tuberculosis is a problematic pathogenic agent, as it is difficult to establish microbiological confirmation of disease in children. Rates of TB infection, as evidenced by Mantoux test positivity, were surprisingly high in cases and controls and there was evidence that ideal timing of a case's Mantoux test would be during or after convalescence from an acute pneumonia episode (see Section 6.3). The limited study of case and control Mantoux reactivity suggests that Mtb may by an important risk factor for acute pneumonia, as cases had an almost 3-fold

higher odds of having a reactive Mantoux **compared to** controls. **A** 907

potential flaw in the methodology was the possible impact of boosting in case follow-up Mantoux responses. Prospective trials of Mantoux testing in the recovery period after acute pneumonia in children, compared to the conventional method of testing during the acute illness, would be warranted in high-burdened settings of child TB. There were 27 (2.9%) microbiologically-confirmed Mtb cases in the South African PERCH cohort, compared to seven (0.8%) MCPP cases: this may suggest a larger

role of Mtb in the pathogenesis of CAP in South African **children** 242

than pneumococcus – this potential outcome will be explored in more detail in the Bayesian analysis of the South African site-specific PERCH publication. It is unfortunate that new rapid molecular techniques were not explored in the South African PERCH study. Studies are underway in South Africa appraising the utility of these techniques, including on stool specimens. 10.1.4Pathogens Implicated in Fatal Pneumonia The PLANS study, although limited in number, highlighted the importance of CMV, P. jirovecii (often found together on molecular and histologic testing) and Klebsiella spp. as being associated with fatal pneumonia at the South African PERCH site. Opportunistic pathogens implicated in fatal pneumonia cases in an era of established access to ART for HIV-infected children is concerning. It may reflect inertia in terms of expediting initiation onto ART in HIV-infected infants. This has been countered to some extent by current WHO and National ART guidelines which encourage early infant

diagnosis of HIV infection and expedited **access to ART** 876

[652, 694]. This is coupled by rigorous antenatal HIV testing in pregnant women in South Africa, so as to catch mothers seroconverting from recently-acquired HIV infection early, in order to limit transmission of infection to their infants in a setting where maternal antenatal HIV seroconversion rates are as high as 3.3% (95% CI, 2.8% to 3.8%) [695]. The number of infants spared from contracting vertically-acquired HIV infection has led to a situation in which there is a growing population of HEU infants, at risk for disease caused by conventional (respiratory viral and bacterial) and opportunistic (CMV and P. jirovecii) infectious agents. Adopting strategies of antenatal vaccination of

pregnant women to protect their infants from influenza, **pertussis** 928

(and ultimately, CMV and RSV when safe, efficacious vaccines become available) would be expected to impact on pneumonia mortality rates in infants in settings such as ours. 10.1.5The Special Case of CMV CMV is an important opportunistic pathogen in

children in sub-Saharan Africa. Strategies of countering **the burden of disease** 535

caused by CMV – especially in infants who

appear to be most vulnerable **to the adverse effects of** 900

CMV infection – are sorely needed. An interesting aspect of CMV infection would be to use a vaccine-probe approach to establish

the burden of CMV **pneumonia** occurring **in** children in **sub-Saharan Africa.** 826

If safe, efficacious CMV vaccines are developed an RCT of such a vaccine in pregnant women would be highly important

to establish the role of CMV in pneumonia aetiology young infants **in** 242

South Africa: the impact of the vaccine may be greater in terms of preventing early infantile pneumonia, than on preventing congenital CMV inclusion disease. PCR of CMV on whole blood appears to be more discriminatory in terms of establishing a link between the pathogen and childhood pneumonia than does PCR of NP/OP swabs. A comprehensive prospective study comparing these tests should be undertaken, ideally using the WHO universal standard strain of CMV in order to determine cut-offs of CMV in clinical specimens which best inform when pathogen detection best predicts disease truly caused by CMV. 10.2Recommendations Good research gives rise to more questions than it can competently answer, and the analyses presented herein are no exception to that rule. This Section highlights avenues for future research that ought to be embarked upon in order more fully to characterise pneumonia aetiology in South African

children under-5 years of age. Such research **is** likely **to** 525

impact favourably on the knowledge base of pneumonia research and have applicability to children in other LMIC settings. 10.2.1Motivation for a Deeper Dive into the PERCH Database The mandate given by the research title

of this thesis was to describe the epidemiology of 529

under-5 pneumonia in children

in South Africa in the era **of** wide-spread **access to** 933

HibCV, PCV and ART. I have done this in broad strokes, using a frequentist case-control approach using the attributable fraction method. This assisted in deriving population-based estimates of

the burden of pneumonia associated with each of **the** organisms tested for **in the** 457

NP/OP and whole blood PCR assays undertaken in cases and controls. Cases with radiologically-confirmed pneumonia were chosen as the focus group of interest, for obvious reasons. The all-site and South African site-specific PERCH databases are, however, likely to contain an abundance of data which would assist in more fully describing pneumonia aetiology in the study site(s). Further analysis of the existing PERCH database needs to be undertaken in order to: 1. Establish individually-attributed estimates of the most likely pneumonia aetiology pathogen (or combination of pathogens) implicated in pneumonia aetiology in individual cases; 2. Use the existing body of evidence to determine what proportion of pneumonia cases were at- tributed by pre-defined pathogen-pathogen combinations (including viral-viral, viral-bacterial, and opportunistic pathogen (i.e., CMV and P. jirovecii) co-infections) in HIV-infected, HEU and HIV-unexposed children; 3. Review the pathogen attributions in children highly likely to have had viral mono-infection or viral-viral co-infection associated pneumonia and compare those to cases with bacterial or viral-bacterial co-infections so as to determine predictive clinico-pathologic associations in these groups. Such an analysis may assist in consolidating management algorithms which may assist in supporting short-course, or early withdrawal of, antibiotic therapy in children highly likely to have viral infections so as to strengthen antibiotic stewardship practice in empiric childhood pneumonia treatment; 4. Interrogate children highly likely to have

had pneumococcal-associated pneumonia in PERCH (for instance, those presenting with high-grade pyrexia, that exhibited rapid and sustained defervescence on empiric antibiotic therapy) and contrast the clinical parameters of these children to those with indolent, slowly-resolving clinical disease; 5. Reappraise the PERCH database molecular test results for K. pneumoniae, to establish the potential burden of pneumonia associated with this pathogen

> **in children <5 years of age,** stratified **by HIV-** infection and -exposure **status.** **92**

10.2.2New Clinical Research Engendered by Findings from This Study Numerous points for new research are to be considered in the light of findings from this series of studies. These include: 1. Given the primacy of RSV-associated pneumonia in the South African (and all-site) PERCH analysis, a Phase 3 RCT of RSV vaccine – when it becomes available – should be conducted as a matter of high importance. The South African PERCH site has substantial experience in terms of conducting vaccine trials, and it would be fitting for the site to be involved in such a

> **trial of RSV vaccine in** young **children,** **625**

or an antenatal

> **trial of RSV vaccine in pregnant women.** **625**

This would afford important evidence for vaccine efficacy in infants in a high-burdened setting of HIV, where a large proportion of the birth cohort is also HEU; 2. The importance of CMV in pneumonia aetiopathogenesis in the sub-Saharan African context has been highlighted in this thesis, and trials evaluating the prevention and treatment of this condition would be important to conduct in a high-burdened HIV setting. Such research should include: (a) An RCT of ganciclovir versus placebo

> **in HIV-infected and** HEU **children** hospitalised **with** hypoxic **pneumonia, in** **827**

order to evaluate clinical outcomes between the groups; (b) An RCT of CMV vaccination versus placebo in the antenatal period, as

> **a vaccine-probe** study **to** determine **the burden of** disease **associated with** **116**

CMV in HIV-infected,

> **HEU and HIV-unexposed infants.** 3. The role **of** **993**

influenza virus in terms of ‘priming’ the respiratory tract for other respiratory pathogens, and precipitating pneumonia requiring hospitalisation in young children

> **is well described in the literature. Studies** should be **conducted in** **111**

order to evaluate this association more fully. For instance: (a) Influenza virus serology testing on archived serum samples from PERCH cases and controls (or archived sera from other case-control pneumonia studies which have been conducted in the past 10 to 15 years) to establish whether there is indeed evidence of a significantly higher burden of preceding influenza virus infection in cases compared to controls; (b) If such an association is appreciated, to conduct an RCT of influenza vaccination compared to placebo

> **in young children, in order to** evaluate to **burden of** **209**

all-cause pneumonia prevented in vaccinees compared to placebo recipients. 4. Evaluate the potential of withholding antibiotic therapy in children highly likely to be hospitalised with viral-associated pneumonia, to see whether outcomes are equivalent to those of children treated empirically with broad-spectrum antibiotic cover in an RCT in a high-burden HIV setting; 5. Establish the utility of point-of-care CRP testing, in conjunction with other clinical markers, in order to assist in shortening or withholding antibiotic therapy in children hospitalised with viral-associated pneumonia. 6. Evaluate the

>

utility and safety of lung aspiration in the diagnosis of pneumonia 715

aetiology in settings other than The Gambia, so as to: (a) Build up clinical competency in this important diagnostic tool for pneumonia aetiology screening, using conventional culture techniques, and molecular assays; (b) Evaluate the molecular diagnostic assessment of the lung microbiome in case-control studies of children dying in hospital and the community from pneumonia and non-infectious causes. 7. Motivate for an RCT of antenatal pertussis vaccination in LMIC settings, to

evaluate the efficacy of this intervention in limiting pneumonia hospitalisation and 927

mortality in infants. 10.2.3Questions Likely to be Answered by Current Ongoing Trials Important clinical trials are currently underway in South Africa, which will probably answer some of the questions raised by this research. These include: 1. The Drakenstein study has been designed as a longitudinal evaluation of paediatric lung health, in which a subset of participants has been intensively sampled to evaluate the nasopharyngeal biome in states of health and disease [314]. This will lead to invaluable analyses of the interplay between bacteria, viruses and fungi preceding and subsequent to upper and lower respiratory tract illness episodes; 2. The Drakenstein study will also serve as an invaluable platform in which to evaluate how LRTI episodes in infancy and young childhood will manifest in terms of chronic disease states (such as allergic asthma) in children. 3. An RCT of co-trimoxazole prophylaxis versus placebo is currently underway in KwaZulu- Natal [661], which will hopefully elucidate avenues for best practice in terms of protecting HEU children from P. jirovecii pneumonia in a setting of high HIV exposure, low

vertical transmission of HIV from mother-to-child, 2

and reasonably high breastfeeding rates; 4. Less invasive sampling for microbiologic confirmation of Mtb infection are being explored in a TB diagnostic study currently underway in the Eastern and Western Cape Provinces of South Africa, which includes an evaluation of stool Xpert® MTB/RIF. This specimen would have great benefit over both IS and GA in terms of the ease of collection at minimal discomfort to young children; 5. A multicentre minimally invasive autopsy study is currently underway, with the South African site being centered at CHBAH. This important study will elucidate in much greater detail than ever before, the aetio-pathogens implicated in fatal pneumonia cases in this high-burdened setting of HIV-infection and -exposure.

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. APPENDICES 309 A Sub-Saharan African Paediatric Pneumonia Studies The studies tabulated in this Appendix cross reference to Section 1.3.2 of this thesis, which highlights the burden of childhood CAP in sub-Saharan Africa. 310 A. Sub-Saharan African Paediatric Pneumonia Studies 311 Tab. A.1: African Hospitalised Paediatric Cohort Studies – Study Site, Time Frame and Patient Characteristics Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Scragg [83] Durban, South Africa Jan 1955 to Dec 1956 24 Retrospective 1 565 (1 520 (97.0%) 2 to 96 <60 months) Musoke [84] Kampala, Uganda Jan to Dec 1959 12 Retrospective 1 380 (853 (62.0%) <72 <60 months) Davidson [85] Lusaka, Zambia Mid-1960s (not stated) Retrospective 2 739 (2 337 (85.0%) <59 <60 months) Wilkinson [87] Segbwema, Sierra Jan 1955 to Dec 1964 120 Retrospective 10 159 (6 974 (69.0%) <180 Leone <60 months) Leary [88] Cape Town, Jan to Dec 1967 12 Retrospective 4 922 (Number <60 <144 South Africa months not stated) Leary [91] Cape Town, Jan to Dec 1967; 36 Retrospective 15 095 (Number <60 <144 South Africa Jan to Dec 1970; months not stated) Jan to Dec 1971 Balint [94] Ndola, Zambia May 1974 to May 1975 12 Retrospective 6 543 (Number <60 Paediatric months not stated) Scragg [95] Durban, South Africa Not stated: 1960s-70s 12 Retrospective 90 (All <60 months) 4 to 60 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 312 Tab. A.1, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Scragg [96] Durban, South Africa Jan 1960 to Dec 1975 192 Retrospective 92 379 (80 255 (87.0%) <144 <60 months) Obi [98] Benin-City, Nigeria Jun 1972 to May 1973 12 Retrospective 3 569 (All <60 months) <60 Stein [99] Johannesburg, Jan to Dec 1978 12 Retrospective 4 687 (Number <60 <168 South Africa months not stated) Berkowitz [103] Johannesburg, Dec 1981 to Nov 1982 12 Prospective 68 (All <60 months) 4 to 53 South Africa Moosa [105] Durban, South Africa Jan to Dec 1980 12 Retrospective 7 688 (Number <60 <168 months not stated) el Tahir Taha [108] Juba, Sudan May to Dec 1984 8 Prospective 144 (Number <60 months <180 not stated) Kabeya [124] White River, Jan to Dec 1982 12 Retrospective 3 956 (Number <60 <144 South Africa months not stated) Kravitz [128] Karoyi District, Jan to Dec 1986 12 Retrospective 801 (Number <60 months Paediatric Zimbabwe not stated) Shimeles [130] Addis Ababa, Ethiopia Jan to Dec 1992 12 Prospective 90 (All <60 months) 4 to 59 Falade [131] Fajara, The Gambia Nov 1990 to Mar 1992 16 Prospective 742 (All <60 months) 3 to 59 Menge [132] Eldoret, Kenya Oct 1991 to Sept 1992 12 Retrospective 2 525 (All <60 months) <60 Menge [132] Eldoret, Kenya Jan to Jun 1993 6 Retrospective 1 504 (Number <60 <180 months not stated) Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 313 Tab. A.1, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Vetter [138] Abidjan, Cote d'Ivoire Aug 1991 to Jul 1992 12 Prospective 4 480 (Number <60 1 to 180 months not stated) Chopra [143] Hlabisa, South Africa Mar 1995 to Feb 1996 12 Prospective 1 364 (995 (73.0%) <144 <60 months) Gernaat [144] Nchelenge, Zambia Jan 1985 to Aug 1988 24 Retrospective 6 412 (Number <60 <180 (1985 to 1987) months not stated) and Prospective (1987 to 1988) Gernaat [145] Nchelenge, Zambia Apr 1987 to Mar 1989 24 Prospective 299 (All <60 months) <60 Zwi [151] Johannesburg, Jan 1992 to Dec 1997 60 Retrospective 22 633 (Number <60 <172 South Africa months not stated) Meyers [161] Johannesburg, Jun to Dec 1996 7 Prospective 549 (All <60 months) <60 South Africa English [177] Kilifi, Kenya Sept 1999 to Aug 2000 12 Prospective 4 020 (3 470 (86.0%) >2 <60 months) Campbell [178] Bamako, Mali Jan to Dec 2000 12 Retrospective 1 644 (Number <60 <180 months not stated) Coutsoudis [181] Durban, South Africa Jul 1995 to Apr 1998 33 Prospective 363 (All <60 months) <60 van Deventer [182] Bloemfontein, Jan to Dec 1991 12 Retrospective 2 251 (Number <60 <144 South Africa months not stated) Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 314 Tab. A.1, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) van Deventer [182] Bloemfontein, Jan to Dec 2001 12 Retrospective 1 836 (Number <60 <144 South Africa months not stated) Uriyo [188] Moshi, Tanzania Jan to Dec 2000 12 Retrospective 1 469 (All <60 months) <60 Uriyo [188] Moshi, Tanzania Jan to Dec 2001 12 Retrospective 1 441 (All <60 months) <60 Jaspan [195] Cape Town, Jan 2002 to Jun 2006 42 Retrospective 141 (Number <60 months 1 to 108 South Africa not stated) Reyburn [80] Multisite: Tanzania Jan to Dec 2004 12 Retrospective 27 703 (Number <60 Paediatric months not stated) Makworo [205] Nairobi, Kenya Not stated 1 Prospective 817 (All <60 months) 0 to 60 Jeena [209] Durban, South Africa Feb 2003 to Feb 2004 12 Prospective 925 (All <60 months) <2 Ekaru [214] Eldoret, Kenya 6 Prospective 181 (All <60 months) <60 Gordon [225] Gondar, Ethiopia Nov 2009 to Nov 2010 12 Prospective 1 352 (All <60 months) 1 to 180 Sigau´que [232] Manhi¸ca, Mozambique Jan 2006 to Dec 2008; 96 Prospective 8 067 (All <60 months) <60 Jan 2010 to Dec 2011 Anonymous [234] Moshi, Tanzania Jan to Dec 2014 12 Prospective 2 609 (All <60 months) <60 Bilkisu [235] Gusau, Nigeria Apr 2013 to Mar 2014 12 Retrospective 801 (520 (65.0%) 1 to 155 <60 months) Divala [236] Karonga, Malawi Jan 2009 to Jun 2011

30 Prospective 7 929 (All <60 months) <60 Kuti [239] Basse, The Gambia Nov 2010 to Apr 2011 6 Prospective 1 517 (All <60 months) 2 to 59 Hospital Cohort Study start year: Total 1 003 Prospective=18; Total 261 449 Studies (n=41) 1955 to 2014 (83.6 years): Retrospective=22; (minimum 131 526 (50.3%) Median 12.0 Both=1 <60 months) (Range, 1.0 to 192.0) Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 315 Tab. A.2: African Hospitalised Paediatric Cohort Studies – Pneumonia Burden and Case Fatality Ratio AuthorStudy Time Period Number with

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Scragg [83] Jan 1955 to Dec 1956 453 28.9 175 38.6 Musoke [84] Jan to Dec 1959 154 154 11.2 32 32 20.8 20.8 Davidson [85] Mid-1960s (not stated) 665 582 24.3 81 77 12.2 13.2 Wilkinson [87] Jan 1955 to Dec 1964 1 850 18.2 218 207 11.8 Leary [88] Jan to Dec 1967 1 955 39.7 Leary [91] Jan to Dec 1967; 5 445 36.1 Jan to Dec 1970; Jan to Dec 1971 Balint [94] May 1974 to May 1975 2 137 32.7 383 17.9 Scragg [95] Not stated: 1960s-70s 27 27 30.0 Scragg [96] Jan 1960 to Dec 1975 24 085 26.1 Obi [98] Jun 1972 to May 1973 882 882 24.7 67 67 7.6 7.6 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 316 Tab. A.2, continued from previous page . . . AuthorStudy Time Period Number with

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Stein [99] Jan to Dec 1978 1 261 26.9 55 4.4 Berkowitz [103] Dec 1981 to Nov 1982 18 18 26.5 Moosa [105] Jan to Dec 1980 3 075 40.0 el Tahir Taha [108] May to Dec 1984 56 38.9 0 0.0 Kabeya [124] Jan to Dec 1982 811 20.5 25 3.1 Kravitz [128] Jan to Dec 1986 801 31.9 Shimeles [130] Jan to Dec 1992 57 57 63.3 19 19 33.3 33.3 Falade [131] Nov 1990 to Mar 1992 213 28.7 Menge [132] Oct 1991 to Sept 1992 805 805 31.9 Menge [132] Jan to Jun 1993 334 22.2 20 6.0 Vetter [138] Aug 1991 to Jul 1992 880 19.6 70 9.0 Chopra [143] Mar 1995 to Feb 1996 384 28.2 27 7.0 Gernaat [144] Jan 1985 to Aug 1988 735 11.5 Gernaat [145] Apr 1987 to Mar 1989 98 98 32.8 25 25 25.5 25.5 Zwi [151] Jan 1992 to Dec 1997 8 352 36.9 251 3.0 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 317 Tab. A.2, continued from previous page . . . AuthorStudy Time Period Number with

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Meyers [161] Jun to Dec 1996 345 345 62.8 12 12 3.5 3.5 English [177] Sept 1999 to Aug 2000 527 13.1 13 2.5 Campbell [178] Jan to Dec 2000 289 17.6 35 12.1 Coutsoudis [181] Jul 1995 to Apr 1998 68 68 18.7 17 17 25.0 25.0 van Deventer [182] Jan to Dec 1991 513 22.8 34 6.6 van Deventer [182] Jan to Dec 2001 621 33.8 85 13.7 Uriyo [188] Jan to Dec 2000 280 280 19.1 32 32 11.4 11.4 Uriyo [188] Jan to Dec 2001 355 355 24.6 50 50 14.1 14.1 Jaspan [195] Jan 2002 to Jun 2006 95 67.4 8 8.4 Reyburn [80] Jan to Dec 2004 6 070 21.9 138 2.3 Makworo [205] Not stated 258 258 31.6 Jeena [209] Feb 2003 to Feb 2004 72 72 7.8 2 2 2.8 2.8 Ekaru [214] 181 181 9.6 10 10 5.5 5.5 Gordon [225] Nov 2009 to Nov 2010 812 652 60.1 51 37 6.3 5.7 Sigau´que [232] Jan 2006 to Dec 2008; 2 180 2 180 27.0 Jan 2010 to Dec 2011 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 318 Tab. A.2, continued from previous page . . . AuthorStudy Time Period Number with

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Anonymous [234] Jan to Dec 2014 299 299 11.5 16 16 5.4 5.4 Bilkisu [235] Apr 2013 to Mar 2014 48 41 6.0 8 8 16.7 19.5 Divala [236] Jan 2009 to Jun 2011 3 116 3 116 39.3 Kuti [239] Nov 2010 to Apr 2011 420 420 27.7 Hospital Cohort Studies (n=41) Study start year: 1955 to 2014 Total 72 082 Total 10 890 Median 26.9 (IQR, 19.5 to 33.0) Total 1 959 Total 611 Median 8.0 (IQR, 4.6 to 14.0) Median 12.3 (IQR, 5.5 to 20.5) CFR = case fatality ratio; IQR = interquartile range; Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 319 Tab. A.3: African Hospitalised Paediatric Pneumonia Studies – Study Site, Time Frame and Patient Characteristics Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Tunbridge [86] Bulawayo, Zimbabwe Jan to Dec 1964 12 Retrospective 397 (All <60 months) <192 Collings [106] Marondera, Zimbabwe Jan 1982 to Dec 1983 24 Retrospective 406 (All <60 months) <36 Fagbule [112] Ilora, Nigeria Jul 1985 to Jun 1986 12 Prospective 330 (299 (91.0%) 0.3 to 168 <60 months) Kravitz [128] Karoyi District, Jan to Mar 1986 12 Retrospective

115 (111 (97.0%) 0.5 to 168 Zimbabwe <60 months) Wafula [148] Nairobi, Kenya Oct 1989 to Feb 1990 4 Prospective 103 (All <60 months) <60 Demers [152] Bangui, Central Jul 1996 to Jun 1997 12 Prospective 530 (All <60 months) <60 African Republic Pepin [165] Bangui, Central Jul 1996 to Jun 1997 12 Prospective 505 (All <60 months) 2 to 59 African Republic Ayieko [212] Multisite: Kenya Mar 2007 to Mar 2008 12 Prospective 3 372 (All <60 months) 2 to 59 Abdulkarim [222] Ilorin, Nigeria July 2010 to June 2011 12 Prospective 167 (161 (96.0%) 1 to 168 <60 months) Enarson [237] Multisite: Malawi Oct 2000 to Dec 2005 63 Prospective 47 228 (All <60 months) <60 Enarson [243] Multisite: Malawi Oct 2000 to Jul 2003 33 Prospective 15 709 (All <60 months) <60 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 320 Tab. A.3, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Kelly [244] Gaborone, Botswana Apr 2012 to Oct 2013 18 Prospective 238 (All <60 months) <24 Le Roux [246] Paarl, South Africa May 2012 to Apr 2014 24 Prospective 55 (All <60 months) <60 Caggiano [251] Igiti, Tanzania Aug 2014 to Apr 2014 9 Prospective 100 (79 (79.0%) <144 <60 months) Hospital Study start year: Total 214 Prospective=11; Total 69 255 Pneumonia 1964 to 2013 (17.8 years): Retrospective=3 (69 193 (99.9%) <60 Studies (n=14) Median 12.0 months) (Range, 4.0 to 63.0) Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 321 Tab. A.4: African Hospitalised Paediatric Pneumonia Studies – Pneumonia Burden and Case Fatality Ratio AuthorStudy Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Tunbridge [86] Jan to Dec 1964 397 352 100.0 183 183 46.1 52.0 Collings [106] Jan 1982 to Dec 1983 406 406 100.0 42 42 10.3 10.3 Fagbule [112] Jul 1985 to Jun 1986 330 299 100.0 32 9.7 Kravitz [128] Jan to Mar 1986 115 111 100.0 6 6 5.2 5.4 Wafula [148] Oct 1989 to Feb 1990 77 77 74.5 Demers [152] Jul 1996 to Jun 1997 395 395 74.5 49 49 12.4 12.4 Pepin [165] Jul 1996 to Jun 1997 378 378 74.9 46 46 12.2 12.2 Ayieko [212] Mar 2007 to Mar 2008 3 372 3 372 100.0 195 195 5.9 5.9 Abdulkarim [222] July 2010 to June 2011 167 161 100.0 11 11 6.6 6.8 Enarson [237] Oct 2000 to Dec 2005 47 228 47 228 100.0 4 605 4 605 9.8 9.8 Enarson [243] Oct 2000 to Jul 2003 15 709 15 709 100.0 1 633 1 633 9.8 9.8 Kelly [244] Apr 2012 to Oct 2013 238 238 100.0 14 14 5.9 5.9 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 322 Tab. A.4, continued from previous page . . . AuthorStudy Time Period Number with Under-5 with Proportion Number of Number of CFR (%) Under-5 Severe or Severe or of those Pneumonia Under-5 Pneumonia Very Severe Pneumonia Very Severe Pneumonia Enrolled with Deaths Pneumonia Deaths CFR (%) Pneumonia (%) Le Roux [246] May 2012 to Apr 2014 55 55 100.0 2 2 3.6 3.6 Caggiano [251] Aug 2014 to Apr 2014 100 79 100.0 11 11.0 Hospital Pneumonia Studies (n=14) Study start year: 1964 to 2013 Total 68 967 Total 68 860 Median 100.0 (IQR, 100.0 to 100.0) Total 6 829 Total 6 786 Median 9.8 (IQR, 5.9 to 11.0) Median 9.8 (IQR, 5.9 to 11.2) CFR = case fatality ratio; IQR = interquartile range; Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 323 Tab. A.5: African Paediatric Intensive Care Unit Pneumonia Studies – Study Site, Time Frame and Patient Characteristics Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Jeena [135] Durban, South Africa Mar 1993 to Mar 1994 12 Prospective 332 (All <60 months) <15 Mathivha [146] Johannesburg, Jan 1992 to Dec 1993 24 Prospective 110 (All <60 months) <63 South Africa Jeena [150] Durban, South Africa Jan 1971 to Dec 1980 120 Retrospective 2 686 (Number <60 <144 months not stated) Jeena [150] Durban, South Africa Jan 1981 to Dec 1990 120 Retrospective 3 333 (Number <60 <144 months not stated) Jeena [150] Durban, South Africa Jan 1991 to Dec 1995 60 Retrospective 1 561 (Number <60 <144 months not stated) Jeena [150] Durban, South Africa Jan 1971 to Dec 1995 300 Retrospective 7 850 (Number <60 <144 months not stated) Kling [157] Cape Town, May 1992 to Jul 1993 15 Prospective 44 (All <60 months) <6 South Africa Delport [168] Pretoria, South Africa Nov 1994 to Oct 1995 12 Prospective 23 (All <60 months) 0.5 to 60 Cowburn [189] Cape Town, Feb 2003 to May 2004 16 Prospective 68 (Number <60 months <85 South Africa not stated) Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 324 Tab. A.5, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Rabie [193] Cape Town, Jan to Dec 2003 12 Retrospective 54 (Number <60 months <156 South Africa not stated) Goussard [204] Cape Town, Apr 2001 to Apr 2005 60 Prospective 25 (All <60 months) <6 South Africa Ghani [215] Cape Town, Apr to Dec 2009 9 Prospective 175 (Number <60 months Median 4.7 South Africa not stated) (IQR, 2.3 to 12.9) Kitchin [217] Pretoria, South Africa Jan 2008 to Dec 2009 24 Prospective 63 (All <60 months) <12 ICU Series (n=10) Study start year: Total 652 Prospective=8; Total 16 324 1971 to 2009 (54.3 years): Retrospective=2 (minimum 597 (3.7%) Median 24.0 <60 months) (Range, 9.0 to 300.0) ICU = intensive care unit; Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 325 Tab. A.6: African Paediatric Intensive Care Unit Pneumonia Studies – Pneumonia Burden and Case Fatality Ratio Author Study Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Pneumonia Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Jeena [135] Mar 1993 to Mar 1994 332 332 100.0 50 50 15.1 15.1 Mathivha [146] Jan 1992 to Dec 1993 110 110 100.0 41 41 37.3 37.3 Jeena [150] Jan 1971 to

Dec 1980 645 24.0 238 36.9 Jeena [150] Jan 1981 to Dec 1990 851 25.5 308 36.2 Jeena [150] Jan 1991 to Dec 1995 620 39.7 198 31.9 Jeena [150] Jan 1971 to Dec 1995 2 116 27.0 744 35.1 Kling [157] May 1992 to Jul 1993 44 44 100.0 5 5 11.4 11.4 Delport [168] Nov 1994 to Oct 1995 23 23 100.0 7 7 30.4 30.4 Cowburn [189] Feb 2003 to May 2004 49 72.1 30 61.2 Rabie [193] Jan to Dec 2003 54 100.0 21 38.9 Goussard [204] Apr 2001 to Apr 2005 25 25 100.0 22 22 88.0 88.0 Ghani [215] Apr to Dec 2009 174 99.4 20 11.5 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 326 Tab. A.6, continued from previous page . . . Author Study Time Period Number with Under-5 with Proportion Number of Number of CFR (%) Under-5 Severe or Severe or of those Pneumonia Under-5 Pneumonia Very Severe Pneumonia Very Severe Pneumonia Enrolled with Pneumonia Deaths Pneumonia Deaths CFR (%) Kitchin [217] Jan 2008 to Dec 2009 63 63 100.0 19 19 30.2 30.2 ICU Series (n=10) Study start year: 1971 to 2009 Total 2 990 Total 597 Median 100.0 (IQR, 39.7 to 100.0) Total 959 Total 144 Median 35.2 (IQR, 30.2 to 37.3) Median 30.3 (IQR, 18.9 to 35.6) CFR = case fatality ratio;

produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 327 Tab. A.7: African Paediatric Pneumonia Aetiology Studies – Study Site, Time Frame and Patient Characteristics Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Ogunbi [89] Lagos, Nigeria 1965 to 1968 36 Not stated 145 (Number <60 months Paediatric not stated) Wesley [90] Durban, South Africa Not stated: 12 Prospective 27 (All <60 months) 5 to 48 early 1970s Silverman [93] Zaria, Nigeria Mid-1970S Prospective 88 (65 (74.0%) 4 to 96 (not stated) <60 months) Joosting [97] Johannesburg, May 1966 to Apr 1972 72 Prospective 2 912 (Number <60 <120 South Africa months not stated) Berkowitz [101] Johannesburg, Sept 1977 to Aug 1978 12 Retrospective 75 (65 (87.0%) <120 South Africa <60 months) Berkowitz [104] Johannesburg, Jan to Dec 1982 12 Retrospective 315 (Number <60 months <120 South Africa not stated) Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 328 Tab. A.7, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Wafula [107] Nairobi, Kenya Oct 1981 to Oct1982 12 Prospective 835 (All <60 months) 0 to 60 Wall [110] Fajara, The Gambia Dec 1982 to Jan 1984 24 Prospective 51 (49 (96.0%) <240 <60 months) Adedoyin [111] Ilora, Nigeria Jun 1985 to Mar 1986 9 Prospective 108 (95 (88.0%) 1 to 168 <60 months) Ikeogu [114] Bulawayo, Zimbabwe Feb to Aug 1987 7 Prospective 40 (Number <60 months 2 to 132 not stated) Forgie [115] Fajara, The Gambia Jun 1987 to May 1988 12 Prospective 90 (All <60 months) <12 Forgie [116] Fajara, The Gambia Aug 1986 to May 1988 22 Prospective 64 (Number <60 months 12 to 108 not stated) Forgie [118] Basse, The Gambia Mar 1987 to Mar 1988 12 Prospective 222 (All <60 months) <60 Tumwine [122] Harare, Zimbabwe Jan 1979 to Dec 1988 120 24 (Number <60 months 6 to 120 not stated) Brewster [123] Banjul, The Gambia 3-year 36 Prospective 9 584 (Number <60 <144 prospective study months not stated) Adegbola [125] Banjul, The Gambia Nov 1990 to Oct 1992 48 Prospective 449 (All <60 months) 3 to 59 Fagbule [126] Pakata District, Jul 1988 to Jul 1999 12 Prospective 86 (All <60 months) 2 to 59 Nigeria Hussey [127] Cape Town, Aug 1991 to Jul 1992 12 Prospective 142 (Number <60 months 1 to 144 South Africa not stated) Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 329 Tab. A.7, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) O' Dempsey [129] Basse, The Gambia Jun 1989 to May 1991 24 Prospective 1 014 (All <60 months) <60 Banya [133] Banjul, The Gambia Jun 1989 to May 1991 24 Prospective 1 399 (All <60 months) <60 O' Dempsey [137] Basse, The Gambia Jun 1989 to May 1991 24 Prospective 103 (All <60 months) <60 Falade [139] Fajara, The Gambia Nov 1990 to Oct 1992 24 Prospective 100 (All <60 months) 3 to 58 Kamiya [141] Blantyre, Malawi 12 Jul to 28 Aug 1995 1.75 Prospective 60 (All <60 months) 1 to 23 Goel [149] Cape Town, Jan 1989 to Dec 1995 84 Retrospective 100 (Number <60 months <65 South Africa not stated) Graham [153] Blantyre, Malawi Jul to Dec 1996 6 Prospective 151 (150 (99.0%) 2 to 59 <60 months) Hussey [155] Cape Town, Jun 1995 to Aug 1996 15 Prospective 1 288 (All <60 months) <24 South Africa Karstaedt [156] Johannesburg, Jul 1986 to Jun 1987 12 Retrospective 62 (Number <60 months <120 South Africa not stated) Karstaedt [156] Johannesburg, Jul 1996 to Jun 1997 12 Retrospective 132 (Number <60 months <120 South Africa not stated) Madhi [158] Johannesburg, Mar 1997 to Feb 1998 12 Prospective 1 165 (All <60 months) 2 to 59 South Africa Madhi [159] Johannesburg, Mar 1997 to Feb 1998 12 Prospective 990 (All <60 months) 2 to 59 South Africa Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 330 Tab. A.7, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Madhi [160] Johannesburg, Mar 1997 to Feb 1998 12 Prospective 225 (Number <60 months <144 South Africa not stated) Zar [162] Cape Town, Jan to Dec 1998 12 Prospective 151 (All <60 months) <23 South Africa Falade [163] Fajara, The Gambia Nov 1990 to Mar 1992 16 Prospective 90 (All <60 months) 3 to 58 Madhi [164] Johannesburg, Mar 1997 to Mar 1999 24 Prospective 268 (All <60 months) 2 to 59 South Africa Zar [166] Cape Town, Jan to Dec 1998 12 Prospective 250 (All <60 months) <60 South Africa Madhi [169] Johannesburg, Mar 1997 to Mar 1999 24 Prospective 80 (All <60 months) <60 South Africa Madhi [171] Johannesburg, Mar 1997 to Mar 1998 12 Prospective 1 186 (All <60 months) 2 to 59 South Africa Madhi [172] Johannesburg, Mar 2000 to Oct 2001 18 Prospective 231 (All <60 months) 1.5 to 42 South Africa Madhi [173] Johannesburg, Mar 1997 to Mar 1999 24 Prospective 116 (All <60 months) 2 to 59 South Africa Echave [176] Saint-Louis, Senegal Mar to May 2000 3 Prospective 114 (All <60 months) 2 to 59 Berkley [180] Kilifi, Kenya Feb 1999 to Dec 2001 35 Prospective 11 847 (Number <60 Median 17 months not stated) (IQR, 7 to 35) Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 331 Tab. A.7, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Bii [184] Nairobi, Kenya Jun 2002 to Jul 2003 12 Prospective 60 (All <60 months) <24

Brent [185] Kilifi, Kenya May to Oct 2003 6 Prospective 1 093 (All <60 months) 2 to 59 Uriyo [188] Moshi, Tanzania Feb to May 2003 4 Prospective 72 (All <60 months) 2 to 59 McNally [192] Durban, South Africa Jan 2001 to Dec 2002 24 Prospective 110 (All <60 months) 1 to 59 McNally [192] Durban, South Africa Jan 2001 to Dec 2002 24 Prospective 358 (All <60 months) 1 to 59 Johnson [196] Ibadan, Nigeria Mid-2000s (not stated) 30 Prospective 419 (All <60 months) 0.5 to 59 Nantanda [197] Kampala, Uganda Dec 2005 to Mar 2006 4 Prospective 157 (All <60 months) 2 to 59 Falade [199] Ibadan, Nigeria Feb 2005 to Jan 2006; 24 Prospective 1 210 (All <60 months) 2 to 59 Jul 2006 to Jun 2007 Nokes [200] Kilifi, Kenya Jan 2002 to Dec 2007 60 Prospective 6 026 (All <60 months) <60 Sigau´que [201] Manhi¸ca, Mozambique Mar 2004 to Mar 2006 24 Prospective 4 838 (All <60 months) 0 to 23 Berkley [202] Kilifi, Kenya Jan to Dec 2007 12 Prospective 759 (Number <60 months 0 to 144 not stated) Digolo [203] Nairobi, Kenya Jun to Sept 2009 4 Prospective 335 (All <60 months) 2 to 59 Morrow [206] Cape Town, Nov 2006 to Aug 2008 21 Prospective 202 (All <60 months) <60 South Africa Schwarz [207] Agogo, Ghana Sept 2007 to Jul 2009 22 Prospective 1 032 (Number <60 2 to 59 months not stated) O' Callaghan-Gordo Manhi¸ca, Mozambique Sept 2006 to Sept 2007 12 Prospective 835 (All <60 months) <60 [210] Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 332 Tab. A.7, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Zampoli [211] Cape Town, Dec 2006 to Jun 2008 18 Prospective 202 (All <60 months) <60 South Africa Cardoso [213] Luanda, Angola May 2009 to Apr 2011 24 Prospective 357 (263 (74.0%) <168 <60 months) Hammitt [216] Kilifi, Kenya Jan to Dec 2010 12 Prospective 810 (All <60 months) 1 to 59 Onyango [219] Kilifi, Kenya Jan 2007 to Dec 2010 48 Prospective 2 002 (Number <60 <144 months not stated) Webb [221] Kilifi, Kenya May 2007 to May 2008 12 Prospective 568 (All <60 months) 2 to 59 Cohen [223] Multisite: Feb 2009 to Dec 2011 23 Prospective 6 338 (All <60 months) <60 South Africa Feikin [224] Asembo, Kenya Mar 2007 to Feb 2010 12 Prospective 1 600 (All <60 months) <60 Hsiao2013 [226] Cape Town, Dec 2006 to Jun 2008 18 Prospective 142 (All <60 months) <60 South Africa Moyes [228] Multisite: Jan 2010 to Dec 2011 24 Prospective 4 275 (All <60 months) <60 South Africa Munywoki [229] Kilifi, Kenya Apr 2006 to May 2010 50 Retrospective 2 813 (All <60 months) <60 Nantanda [230] Kampala, Uganda Aug 2011 to Jun 2012 12 Prospective 614 (All <60 months) 2 to 59 Agweyu [233] Nairobi, Kenya Jun to Oct 2009 5 Prospective 385 (All <60 months) 2 to 59 Morrow [240] Cape Town, Nov 2006 to Aug 2009 21 Prospective 202 (All <60 months) <60 South Africa Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 333 Tab. A.7, continued from previous page . . . Author Study Site Study Time Period Study Duration (months) Type of Study Number of Children Enrolled Age Range (months) Cohen [242] Multisite: Feb 2009 to Dec 2012 35 Prospective 8 723 (All <60 months) <60 South Africa Lagare [245] Niamey, Niger Jan 2010 to Dec 2012 24 Prospective 160 (All <60 months) <60 Ma¨ınassara [247] Niamey, Niger Apr 2009 to Apr 2013 48 Prospective 849 (788 (93.0%) <168 <60 months) Zash [249] Multisite: Botswana Mar 2001 to Oct 2005 54 Prospective 85 (All <60 months) <60 Zar [250] Paarl, South Africa May 2012 to Dec 2014 30 Prospective 92 (All <60 months) <19 Hospitalised Study start year: Total 1 389.75 Prospective=66; Total 86 358 Aetiology Cohort 1965 to 2012 (115.8 years): Retrospective=5; (minimum 57 938 (67.1%) (n=73) Median 18.0 Both=2 <60 months) (Range, 1.8 to 120.0) Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 334 Tab. A.8: African Paediatric Pneumonia Aetiology Studies – Pneumonia Burden and Case Fatality Ratio AuthorStudy Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Ogunbi [89] 1965 to 1968 103 71.0 Wesley [90] Not stated: 27 27 100.0 5 5 18.5 18.5 early 1970s Silverman [93] Mid-1970S 88 65 100.0 4 4.5 (not stated) Joosting [97] May 1966 to Apr 1972 2 912 100.0 Berkowitz [101] Sept 1977 to Aug 1978 46 61.3 12 26.1 Berkowitz [104] Jan to Dec 1982 77 24.4 Wafula [107] Oct 1981 to Oct1982 668 668 80.0 Wall [110] Dec 1982 to Jan 1984 51 49 100.0 1 2.0 Adedoyin [111] Jun 1985 to Mar 1986 108 95 100.0 Ikeogu [114] Feb to Aug 1987 40 100.0 1 1 2.5 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 335 Tab. A.8, continued from previous page . . . AuthorStudy Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Forgie [115] Jun 1987 to May 1988 90 100.0 6 6.7 Forgie [116] Aug 1986 to May 1988 64 100.0 2 3.1 Forgie [118] Mar 1987 to Mar 1988 222 100.0 Tumwine [122] Jan 1979 to Dec 1988 24 100.0 6 25.0 Brewster [123] 3-year prospective 1 040 10.9 156 15.0 study Adegbola [125] Nov 1990 to Oct 1992 278 61.9 Fagbule [126] Jul 1988 to Jul 1999 86 86 100.0 0 0.0 Hussey [127] Aug 1991 to Jul 1992 35 24.6 5 14.3 O' Dempsey [129] Jun 1989 to May 1991 1 014 100.0 Banya [133] Jun 1989 to May 1991 1 380 1 380 98.6 O' Dempsey [137] Jun 1989 to May 1991 81 81 78.6 1 1.2 Falade [139] Nov 1990 to Oct 1992 100 100 100.0 Kamiya [141] 12 Jul to 28 Aug 1995 60 60 100.0 14 14 23.3 23.3 Goel [149] Jan 1989 to Dec 1995 100 100.0 7 7.0 Graham [153] Jul to Dec 1996 150 150 99.3 33 33 22.0 22.0 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 336 Tab. A.8, continued from previous page . . . AuthorStudy Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Hussey [155] Jun 1995 to Aug 1996 797 797 61.9 24 3.0 Karstaedt [156] Jul 1986 to Jun 1987 37 59.7 7 18.9 Karstaedt [156] Jul 1996 to Jun 1997 94 71.2 18 19.1 Madhi [158] Mar 1997 to Feb 1998 1 165 1 165 100.0 85 85 7.3 7.3 Madhi [159] Mar 1997 to Feb 1998 990 990 100.0 71 71 7.2 7.2 Madhi [160] Mar 1997 to Feb 1998 131 58.2 20 15.3 Zar [162] Jan to Dec 1998 151 151 100.0 22 22 14.6 14.6 Falade [163] Nov 1990 to Mar 1992 90 90 100.0 Madhi [164] Mar 1997 to Mar 1999 268 268 100.0 7 7 2.6 2.6 Zar [166] Jan to Dec 1998 250 250 100.0 39 39 15.6 15.6 Madhi [169] Mar 1997 to Mar 1999 80 80 100.0 5 5 6.2 6.2 Madhi [171] Mar 1997 to Mar 1998 1 186 1 186 100.0 70 70 5.9 5.9 Madhi [172] Mar 2000 to Oct 2001 231 231 100.0 39 39 16.9 16.9 Madhi [173] Mar 1997 to Mar 1999 116 116 100.0 4 4 3.4 3.4 Echave [176] Mar to May 2000 12 12 10.5 4 4 33.3 33.3 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 337 Tab. A.8, continued from previous page . . . AuthorStudy Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Berkley [180] Feb 1999 to Dec 2001 2 803 23.7 123 4.4 Bii [184] Jun 2002 to Jul 2003 60 60 100.0 Brent [185] May to Oct 2003 128 128 11.7 Uriyo [188] Feb to May 2003 72 72 100.0 9 9 12.5 12.5 McNally [192] Jan 2001 to Dec 2002 110 110 100.0 McNally [192] Jan 2001 to Dec 2002 358 358 100.0 54 15.1 Johnson [196] Mid-2000s (not stated) 323 323 77.1 35 35 10.8 10.8 Nantanda [197] Dec 2005 to Mar 2006 157 100.0 16 10.2 Falade [199] Feb 2005 to Jan 2006; 402 402 33.2 0 0.0 Jul 2006 to Jun 2007 Nokes [200] Jan 2002 to Dec 2007 6 026 6 026 100.0 265 265 4.4 4.4 Sigau´que [201] Mar 2004 to Mar 2006 757 757 15.6 76 76 10.0 10.0 Berkley [202] Jan to Dec 2007 759 100.0 24 3.2 Digolo [203] Jun to Sept 2009 335 335 100.0 26 26 7.8 7.8 Morrow [206] Nov 2006 to Aug 2008 202 202 100.0 51 51 25.2 25.2 Schwarz [207] Sept 2007 to Jul 2009 173 173 16.8 10 10 5.8 5.8 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 338 Tab. A.8, continued from previous page . . . AuthorStudy Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) O' Callaghan-Gordo Sept 2006 to Sept 2007 835 835 100.0 33 33 4.0 4.0 [210] Zampoli [211] Dec 2006 to Jun 2008 200 200 99.0 51 51 25.5 25.5 Cardoso [213] May 2009 to Apr 2011 357 263 100.0 Hammitt [216] Jan to Dec 2010 810 810 100.0 32 32 4.0 4.0 Onyango [219] Jan 2007 to Dec 2010 2 002 100.0 88 4.4 Webb [221] May 2007 to May 2008 568 568 100.0 34 34 6.0 6.0 Cohen [223] Feb 2009 to Dec 2011 6 338 6 338 100.0 Feikin [224] Mar 2007 to Feb 2010 1 600 1 600 100.0 47 47 2.9 2.9 Hsiao2013 [226] Dec 2006 to Jun 2008 142 142 100.0 Moyes [228] Jan 2010 to Dec 2011 4 275 4 275 100.0 83 83 1.9 1.9 Munywoki [229] Apr 2006 to May 2010 1 700 1 700 60.4 Nantanda [230] Aug 2011 to Jun 2012 380 61.9 Agweyu [233] Jun to Oct 2009 385 385 100.0 23 23 6.0 6.0 Morrow [240] Nov 2006 to Aug 2009 202 202 100.0 51 51 25.2 25.2 Cohen [242] Feb 2009 to Dec 2012 8 723 8 723 100.0 150 150 1.7 1.7 Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 339 Tab. A.8, continued from previous page . . . AuthorStudy Time Period Number with

Severe or Very Severe Pneumonia Under-5 with **Severe or Very Severe Pneumonia** 7

Proportion of those Enrolled with Number of Pneumonia Deaths Number of Under-5 Pneumonia Deaths CFR (%) Under-5 Pneumonia CFR (%) Pneumonia (%) Lagare [245] Jan 2010 to Dec 2012 160 160 100.0 Ma¨ınassara [247] Apr 2009 to Apr 2013 849 788 100.0 Zash [249] Mar 2001 to Oct 2005 85 85 100.0 Zar [250] May 2012 to Dec 2014 92 92 100.0 3 3 3.3 3.3 Hospitalised Aetiology Cohort (n=73) Study start year: 1965 to 2012 Total 56 893 Total 44 209 Median 100.0 (IQR, 74.2 to 100.0) Total 1 954 Total 1 378 Median 6.7 (IQR, 3.3 to 15.3) Median 7.2 (IQR, 4.1 to 16.6) CFR = case fatality ratio; IQR = interquartile range; Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 340 Tab. A.9: Sub-Saharan African Studies included in Paediatric Pneumonia Proportion of Admissions Random Effects Meta-analysis (See Figure 1.3) Summary Analysis Explanation of Study Inclusion in the Analysis Number of Studies References A. Hospital Cohort Studies Analysis restricted to studies detailing the clinical spectrum of disease observed in children hospitalised in Paediatric units in sub-Saharan Africa 41 [80, 83–85, 87, 88, 91, 94–96, 98, 99, 103, 105, 108, 124, 128, 130–132, 138, 143–145, 151, 161, 177, 178, 181, 182, 188, 195, 205, 209, 214, 225, 232, 234–236, 239] B. Hospital Cohort Studies (<5 years) As for 'A', but focussing in children <5 years of age 20 [84, 85, 95, 98, 103, 130, 132, 145, 161, 181, 188, 205, 209, 214, 225, 232, 234–236, 239] C. Hospital Mortality Profile Selecting out studies describing the disease spectrum in children dying in hospital 15 [92, 109, 113, 119, 134, 136, 140, 167, 174,

189, 203, 208, 227, 231, 238] D. Hospital Mortality Profile (<5 years) As for ‘C’, but focussing in children <5 years of age 8 [109, 113, 119, 134, 203, 227, 231, 238] Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 341 Tab. A.9, continued from previous page . . . Summary Analysis Explanation of Study Inclusion in the Analysis Number of Studies References E. Studies with available data on Inclusive of all studies that reported the 56 [80, 83–85, 87, 88, 91, 92, 94–96, 98, 99, 103, 105, proportion of paediatric number of paediatric hospitalisations and/ or 108, 109, 113, 119, 124, 128, 130–132, 134, 136, 138, admissions or in-hospital deaths and number of children with a clinical 140, 143–145, 151, 161, 167, 174, 177, 178, 181, 182, deaths associated with diagnosis of pneumonia 188, 189, 195, 203, 205, 208, 209, 214, 225, 227, 231, pneumonia 232, 234–236, 238, 239] Table produced using the stargazer package in R [66]. A. Sub-Saharan African Paediatric Pneumonia Studies 342 Tab. A.10: Sub-Saharan African Studies included in Paediatric Pneumonia Case Fatality Ratio Random Effects Meta-analysis (See Figure 1.4) Summary Analysis Explanation of Study Inclusion in the Analysis Number of Studies References A. Hospital Cohort Studies Analysis restricted to studies detailing the 28 [80, 83–85, 87, 94, 98, 99, 108, 124, 130, 132, 138, clinical spectrum of disease observed in 143, 145, 151, 161, 177, 178, 181, 182, 188, 195, 209, children hospitalised in Paediatric units in 214, 225, 234, 235] sub-Saharan Africa B. Hospital Cohort Studies As for ‘A’, but excluding studies describing 24 [80, 84, 85, 87, 94, 98, 99, 108, 124, 130, 132, 138, 143, (not malnourished) the spectrum of disease in malnourished 151, 161, 177, 178, 182, 188, 195, 209, 225, 234, 235] children C. Hospital Cohort Studies As for ‘A’, but selecting out studies 2 [83, 145] (malnourished) describing the disease spectrum in malnourished children only Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 343 Tab. A.10, continued from previous page . . . Summary Analysis Explanation of Study Inclusion in the Analysis Number of Studies References D. Combined Studies Includes studies which described the clinical 29 [138, 141, 153, 158–162, 164, 166, 169, 171–173, 181, (HIV-infected) course of disease in HIV-infected children, 186–188, 191, 201, 206, 209–211, 225, 228, 240, 244, except those describing children admitted to 246] ICU and studies describing cause of death amongst paediatric patients E. Combined Studies Includes studies which described the clinical 28 [138, 141, 153, 158–161, 164, 166, 169, 171–173, 181, (HIV-uninfected) course of disease in HIV-uninfected children, 186–188, 191, 201, 206, 209–211, 225, 228, 240, 244, except those describing children admitted to 246] ICU and studies describing cause of death amongst paediatric patients F. Pneumonia Cohort Studies Analysis restricted to studies which described 13 [86, 106, 112, 128, 152, 165, 212, 222, 237, 243, 244, the course of children hospitalised with 246, 251] clinically diagnosed pneumonia G. Pneumonia Aetiology Studies Includes studies which sought to identify the 52 [90, 93, 101, 110, 114–116, 122, 123, 126, 127, 137, aetiologic cause of pneumonia in the 141, 147, 149, 153, 155, 156, 158–160, 162, 164, 166, paediatric age group 169, 171–173, 176, 180, 188, 192, 196, 197, 199–203, 206, 207, 210, 211, 216, 219, 221, 224, 228, 233, 240, 242, 250] Continued on next page . . . A. Sub-Saharan African Paediatric Pneumonia Studies 344 Tab. A.10, continued from previous page . . . Summary Analysis Explanation of Study Inclusion in the Analysis Number of Studies References H. ICU Cohort Studies Includes studies describing the clinical course 10 [135, 146, 150, 157, 168, 189, 193, 204, 215, 217] of children admitted to ICU with a diagnosis of CAP I. Studies with available CFR Inclusive of all studies that reported the 99 [72, 80, 83–87, 90, 93, 94, 98, 99, 101, 106, 108, 110, data number of pneumonia deaths and number of 112, 114–116, 122–124, 126–128, 130, 132, 137, 138, children with a clinical diagnosis of 141, 143, 145, 147, 149, 151–153, 155, 156, 158–162, pneumonia, excluding studies focussed on 164–166, 169, 171–173, 175–178, 180–182, 186–188, children admitted to ICU 191, 192, 195–203, 206, 207, 209–212, 214, 216, 219–222, 224, 225, 228, 233–235, 237, 240, 242–244, 246, 250, 251]

Table produced using the stargazer package in R [66]. B Microbiology and Virology Results from African Child Pneumonia Aetiology Studies The table in this Appendix reference to Subsection 1.4.4 of this thesis, and selects out studies that detail blood culture (Table B.1), sputum bacterial culture (Table B.2), sputum PCR and IFA results (Table B.3) and LA culture results (Table B.4). Furthermore, studies detailing bacteriology and virology results from testing of upper respiratory tract secretions are included here (Tables B.5 and B.7). 345 Tab. B.1: African Paediatric Pneumonia Aetiology Studies – Blood Culture Results Author Total BC ACINE (n, %) ECOL (n, %) GAS (n, %) HINFL (n, %) KLEBS (n, %) PNEU (n, %) PNEU & HINFL (n, %) PSEU (n, %) SASP (n, %) SAUR (n, %) Other bacteria (n, %) Other Gram Neg (n, %) Other Gram Pos (n, %) Silverman [93] 36 4 (11.1) Berkowitz [101] 46 1 (2.2) 3 (6.5) 46 1 (2.2) (100.0) Berkowitz [104] 77 2 (2.6) 12 (15.6) 2 (2.6) 46 (59.7) 2 (2.6) 7 (9.1) 4 (5.2) 1 (1.3) 1 (1.3) Wafula [107] 449 4 (0.9) 1 (0.2) 6 (1.3) 5 (1.1) 1 (0.2) 2 (0.4) 17 (3.8) 7 (1.6) 6 (1.3) Wall [110] 64 4 (6.2) 13 (20.3) Forgie [115] 81 3 (3.7) 5 (6.2) 1 (1.2) Forgie [116] 74 1 (1.4) 10 (13.5) 1 (1.4) 1 (1.4) Adegbola [125] 278 1 (0.4) 7 (2.5) 1 (0.4) 17 (6.1) 5 (1.8) 2 (0.7) 2 (0.7) Fagbule [126] 73 14 (19.2) 4 (5.5) 25 (34.2) Hussey [127] 35 35 (100.0) O’ Dempsey [129] 1 014 1 (0.1) 12 (1.2) 45 (4.4) 1 (0.1) 12 (1.2) 3 (0.3) 1 (0.1) Banya [133] 1 222 3 (0.2) 15 (1.2) 45 (3.7) 26 (2.1) 3 (0.2) 2 (0.2) 2 (0.2) Falade [139] 100 4 (4.0) 1 (1.0) 11 (11.0) 2 (2.0) 1 (1.0) Continued on next page . . . 346 Author Total BC ACINE (n, %) ECOL (n, %) GAS (n, %) HINFL (n, %) KLEBS (n, %) PNEU (n, %) PNEU & HINFL (n, %) PSEU (n, %) SASP (n, %) SAUR (n, %) Other bacteria (n, %) Other Gram Neg (n, %) Other Gram Pos (n, %) Goel [149] 98 23 (23.5) Graham [153] 150 0 (0.0) 0 (0.0) 0 (0.0) 3 (2.0) 0 (0.0) 8 (5.3) 0 (0.0) 7 (4.7) 0 (0.0) 2 (1.3) 1 (0.7) Karstaedt [156] 37 37 (100.0) Karstaedt [156] 94 94 (100.0) Madhi [158] 1 165 8 (0.7) 30 (2.6) 2 (0.2) 58 (5.0) 6 (0.5) 14 (1.2) 3 (0.3) 2 (0.2) Madhi [160] 225 225 (100.0) Madhi [164] 266 8 (3.0) 3 (1.1) 1 (0.4) Zar [166] 244 3 (1.2) 3 (1.2) 2 (0.8) 12 (4.9) 3 (1.2) 2 (0.8) 5 (2.0) 3 (1.2) 2

(0.8) Madhi [169] 80 1 (1.2) 2 (2.5) 2 (2.5) Madhi [171] 1 022 25 (2.4) 38 (3.7) Madhi [172] 231 4 (1.7) 1 (0.4) 6 (2.6) 1 (0.4) 2 (0.9) 2 (0.9) 1 (0.4) Madhi [173] 116 1 (0.9) 3 (2.6) 1 (0.9) 2 (1.7) Berkley [180] 2 803 9 (0.3) 16 (0.6) 3 (0.1) 29 (1.0) 2 (0.1) 71 (2.5) 4 (0.1) 36 (1.3) 6 (0.2) 8 (0.3) 5 (0.2) McNally [192] 358 1 (0.3) 3 (0.8) 2 (0.6) 2 (0.6) 26 (7.3) 1 (0.3) 1 (0.3) 16 (4.5) 2 (0.6) 32 (8.9) Continued on next page . . . 347 Author Total BC ACINE (n, %) ECOL (n, %) GAS (n, %) HINFL (n, %) KLEBS (n, %) PNEU (n, %) PNEU & HINFL (n, %) PSEU (n, %) SASP (n, %) SAUR (n, %) Other bacteria (n, %) Other Gram Neg (n, %) Other Gram Pos (n, %) Johnson [196] 205 9 (4.4) 3 (1.5) 1 (0.5) 5 (2.4) 22 (10.7) 6 (2.9) 1 (0.5) Nantanda [197] 157 2 (1.3) 3 (1.9) 7 (4.5) 4 (2.5) 9 (5.7) Falade [199] 399 2 (0.5) 2 (0.5) 14 (3.5) 9 (2.3) 6 (1.5) 11 (2.8) 44 (11.0) 2 (0.5) Nokes [200] 5 935 81 (1.4) 16 (0.3) 81 (1.4) 48 (0.8) 64 (1.1) 16 (0.3) 16 (0.3) Sigau´que [201] 613 14 (2.3) 22 (3.6) 20 (3.3) 9 (1.5) 25 (4.1) Berkley [202] 759 3 (0.4) 9 (1.2) 3 (0.4) 1 (0.1) 12 (1.6) 3 (0.4) 3 (0.4) 2 (0.3) Digolo [203] 335 2 (0.6) 5 (1.5) 1 (0.3) 3 (0.9) Morrow [206] 202 2 (1.0) 1 (0.5) 3 (1.5) 1 (0.5) 3 (1.5) 1 (0.5) 8 (4.0) Schwarz [207] 173 1 (0.6) 1 (0.6) 2 (1.2) 8 (4.6) 1 (0.6) 20 (11.6) 5 (2.9) 1 (0.6) 1 (0.6) O' Callaghan-Gordo 345 11 (3.2) 11 (3.2) 4 (1.2) 12 (3.5) [210] Hammitt [216] 749 4 (0.5) 4 (0.5) 3 (0.4) 30 (4.0) 6 (0.8) 1 (0.1) 3 (0.4) 1 (0.1) Webb [221] 568 1 (0.2) 5 (0.9) 3 (0.5) 1 (0.2) 15 (2.6) 2 (0.4) 3 (0.5) 2 (0.4) Feikin [224] 608 1 (0.2) 5 (0.8) 11 (1.8) 3 (0.5) Agweyu [233] 338 2 (0.6) 5 (1.5) 1 (0.3) 3 (0.9) Cohen [242] 3 196 2 (0.1) 3 (0.1) 7 (0.2) 18 (0.6) 2 (0.1) 38 (1.2) 3 (0.1) 2 (0.1) Zash [249] 61 1 (1.6) 1 (1.6) 1 (1.6) 1 (1.6) 1 (1.6) 1 (1.6) Continued on next page . . . 348 Author Total BC ACINE ECOL GAS HINFL KLEBS PNEU PNEU & PSEU SASP SAUR Other Other Other

(n, %) (n, %) (n, %) (n, %) (n, %) (n, %) HINFL **(n, %) (n, %) (n, %) (n,** %) bacteria **(n,** %) Gram Neg **(n,** %) Gram Pos **(n,** %) Zar [250] 90 **1 (1.1)**

Total 25 171 97 (0.4) 92 (0.4) 90 (0.4) 278 (1.1) 74 (0.3) 1 056 16 (0.1) 42 (0.2) 202 (0.8) 275 (1.1) 45 (0.2) 49 (0.2) 59 (0.2) (4.2) ACINE = Acinetobacter spp.; BC = blood culture; ECOL = E. coli ; GAS = Group A β-haemolytic streptococcus;

Gram Neg = Gram negative; Gram Pos = Gram positive;

HINFL = H. influenzae ; KLEBS = Klebsiella spp.; PNEU = S. pneumoniae ; PSEU = Pseudomonas spp.; SASP = Salmonella spp.; SAUR = S. aureus ; Table produced using the stargazer package in R [66]. 349 Tab. B.2: African Paediatric Pneumonia Aetiology Studies – Sputum Culture Results Author Total Sputum ACINE (n, %) ECOL (n, %) GAS (n, %) HINFL (n, %) KLEBS (n, %) MCAT (n, %) Mtb (n, %) PNEU (n, %) PSEU (n, %) SASP (n, %) SAUR (n, %) Other Gram Neg (n, %) Other Gram Pos (n, %) Silverman [93] 72 15 (20.8) Tumwine [122] 19 1 (5.3) 4 (21.1) 2 (10.5) 3 (15.8) 8 (42.1) 1 (5.3) Adegbola [125] 26 9 (34.6) 3 (11.5) Zar [166] 243 10 (4.1) 25 (10.3) 30 (12.3) 9 (3.7) 19 (7.8) 6 (2.5) 15 (6.2) 25 (10.3) Bii [184] 60 11 (18.3) 2 (3.3) 26 (43.3) 3 (5.0) 2 (3.3) 8 (13.3) 2 (3.3) Nantanda [197] 157 13 (8.3) 20 (12.7) 19 (12.1) 4 (2.5) 39 (24.8) 3 (1.9) 1 (0.6) 9 (5.7) 4 (2.5) 2 (1.3) Hammitt [216] 417 4 (1.0) 14 (3.4) 3 (0.7) 16 (3.8) 2 (0.5) 16 (3.8) 3 (0.7) 1 (0.2) 2 (0.5) Morrow [240] 202 Total 1 196 10 (0.8) 29 (2.4) 4 (0.3) 61 (5.1) 89 (7.4) 29 (2.4) 21/660 79 (6.6) 29 (2.4) 1 (0.1) 51 (4.3) 8 (0.7) 3 (0.3) (3.2) a The study by Hammitt et al [216] reported the culture results of 59 (84.3%) of 70 sputum cultures, deemed to be of adequate quality (Bartlett score >0) to attribute aetiology. ACINE = Acinetobacter spp.; ECOL = E. coli ; GAS = Group A β-haemolytic streptococcus;

Gram Neg = Gram negative; Gram Pos = Gram positive;

HINFL = H. influenzae ; KLEBS = Klebsiella spp.; MCAT = M. catarrhalis ; Mtb = M. tuberculosis ; PNEU = S. pneumoniae ; PSEU = Pseudomonas spp.; SASP = Salmonella spp.; SAUR = S. aureus ; Table produced using the stargazer package in R [66]. 350 Tab. B.3: African Paediatric Pneumonia Aetiology Studies – Sputum IFA & PCR Results Author Total Sputum CMV PCR (n, %) PJP PCR (n, %) PJP IFA (n, %) PNEU PCR (n, %) Mtb PCR (n, %) Zar [166] 243 19 (7.8) Bii [184] 60 8 (13.3) Nantanda [197] 157 2 (1.3) 46 (29.3) 1 (0.6) Morrow [240] 202 45 (22.3) 109 (54.0) 43 (21.3) Total 662 45/202 111/359 70/505 46/157 1/157 (0.6) (22.3) (30.9) (13.9) (29.3) CMV = human cytomegalovirus; IFA = indirect fluorescent antibody; Mtb = M. tuberculosis ; PCR = polymerase chain reaction; PJP = P. jirovecii ; PNEU = S. pneumoniae ; Table produced using the stargazer package in R [66]. 351 Tab. B.4: African Paediatric Pneumonia Aetiology Studies – Lung Aspirate Results Author Total LA ECOL (n, %) GAS (n, %) HINFL (n, %) KPNE (n, %) MCAT (n, %) Mtb (n, %) PNEU (n, %) PSEU (n, %) SASP (n, %) SAUR (n, %) Other Gram Neg (n, %) Other Gram Pos (n, %) Mixed growth (n, %) Wesley [90] 27 8 (29.6) 4 (14.8) 11 (40.7) 1 (3.7) 4 (14.8) Silverman [93] 88 5 (5.7) 9 (10.2) 31 (35.2) 1 (1.1) 8 (9.1) 7 (8.0) 6 (6.8) Wall [110] 64 7 (10.9) 21 (32.8) Adedoyin [111] 108 6 (5.6) 14 (13.0) 18 (16.7) 4 (3.7) 22 (20.4) 8 (7.4) Ikeogu [114] 40 2 (5.0) 1 (2.5) 6 (15.0) 3 (7.5) 2 (5.0) Forgie [116] 29 10 (34.5) 3 (10.3) Adegbola [125]a 94 8 (8.5) 31 (33.0) 2 (2.1) 1 (1.1) 1 (1.1) Fagbule [126] 73 12 (16.4) 5 (6.8) 33 (45.2) O' Dempsey 16 4 (25.0) [129] Falade [139] 100 1 (1.0) 8 (8.0) 1 (1.0) 4 (4.0) 31 (31.0) 2 (2.0) 1 (1.0) 1 (1.0) 3 (3.0) Johnson [196] 13 3 (23.1) 1 (7.7) Total 652 14 (2.1) 6 (0.9) 34 (5.2) 29 (4.4) 1 (0.2) 5 (0.8) 157 9 (1.4) 1 (0.2) 84 (12.9) 18 (2.8) 12 (1.8) 5 (0.8) (24.1) a The study by Adegbola et al [125] also investigated for viral pathogens in LA specimens using cell culture and rapid indirect immunofluorescence: in the 94 LA specimens, 10 (10.6%) were positive for adenovirus, six (6.4%) for influenza A, four (4.3%) for RSV, three (3.2%) for parainfluenza viruses and one (1.1%) for influenza B. ECOL = E. coli ; GAS = Group A β-haemolytic streptococcus;

Gram Neg = Gram negative; Gram Pos = Gram positive; 406

HINFL = H. influenzae ; KPNE = K. pneumoniae ; LA = lung aspirate; MCAT = M. catarrhalis ; Mtb = M. tuberculosis ; PNEU = S. pneumoniae ; PSEU = Pseudomonas spp.; SASP = Salmonella spp.; SAUR = S. aureus ; Table produced using the stargazer package in R [66]. 352 Tab. B.5: African Paediatric Pneumonia Aetiology Studies – Nasopharyngeal Aspirate Bacteriology Results Author Total NP BOPE (n, %) CPNEU (n, %) ECOL (n, %)

HIB (n, %) HINF **(n,** %) HINFL **(n,** %) KLEBS **(n,** %) MPNEU **(n,** %) PNEU **(n,** %) PSEU **(n,** %) SAUR **(n,** %) Other **(n,** 728

%) Wafula [107] 498 3 (0.6) 13 (2.6) 23 (4.6) 21 (4.2) 22 (4.4) 75 (15.1) 3 (0.6) 29 (5.8) 14 (2.8) Hammitt [216] 805 3 (0.4) Feikin [224] 350 2 (0.6) Lagare [245] 160 4 (2.5) 20 (12.5) 90 (56.2) 18 (11.2) Zash [249] 50 1 (2.0) Total 1 863 4/548 4/160 13/498 20/160 23/498 21/498 22/498 5/1 155 165/658 3/498 47/658 14/498 (0.7) (2.5) (2.6) (12.5) (4.6) (4.2) (4.4) (0.4) (25.1) (0.6) (7.1) (2.8) BOPE = B. pertussis ; CPNEU = C. pneumoniae ; ECOL = E. coli ;

HIB = H. influenzae type b; HINF = non **-type** b **H. influenzae** 36

; HINFL = H. influenzae ; KLEBS = Klebsiella spp.; MPNEU = M. pneumoniae ; PNEU = S. pneumoniae ; PSEU = Pseudomonas spp.; SAUR = S. aureus ; Table produced using the stargazer package in R [66]. 353 Tab. B.6: African Paediatric Pneumonia Aetiology Studies – Nasopharyngeal Aspirate Virology Results 1 Author Total NP ADENO (n, %) CMV (n, %) COR

(n, %) EV PCR **(n,** %) FLU **(n,** %) FLUA **(n,** %) FLUB **(n,** %) FLUC **(n,** %) HBOV **(n,** %) HMPV **(n,** 341

%) HSV (n, %) Joosting [97] 2 912 111 (3.8) 37 (1.3) 66 (2.3) 17 (0.6) 7 (0.2) 156 (5.4) Forgie [115] 86 4 (4.7) 37 (43.0) 3 (3.5) 1 (1.2) Forgie [116] 67 14 (20.9) Forgie [118] 221 13 (5.9) 8 (3.6) Adegbola [125] 448 40 (8.9) 8 (1.8) 4 (0.9) Kamiya [141] 60 Hussey [155] 162 6 (3.7) 1 (0.6) Zar [166] 243 31 (12.8) Madhi [172] 231 1 (0.4) 6 (2.6) Madhi [173] 116 116 (100.0) 97 (83.6) 20 (17.2) McNally [192] 110 9 (8.2) 44 (40.0) Johnson [196] 122 9 (7.4) 16 (13.1) 3 (2.5) Berkley [202] 759 29 (3.8) 76 (10.0) 44 (5.8) 1 (0.1) 16 (2.1) 23 (3.0) Morrow [206] 199 18 (9.0) 74 (37.2) O' Callaghan-Gordo 807 102 (12.6) 18 (2.2) 21 (2.6) 18 (2.2) 39 (4.8) [210] Cardoso [213] 357 21 (5.9) 13 (3.6) 4 (1.1) Continued on next page . . . 354 Tab. B.6, continued from previous page . . . Author Total NP ADENO (n, %) CMV (n, %) COR

(n, %) EV PCR **(n,** %) FLU **(n,** %) FLUA **(n,** %) FLUB **(n,** %) FLUC **(n,** %) HBOV **(n,** %) HMPV **(n,** 341

%) HSV (n, %) Hammitt [216] 805 39 (4.8) 43 (5.3) 12 (1.5) 7 (0.9) 2 (0.2) 3 (0.4) 25 (3.1) Onyango [219] 2 002 99 (4.9) 71 (3.5) 19 (0.9) 11 (0.5) Webb [221] 480 Cohen [223] 6 338 518 (8.2) Feikin [224] 350 52 (14.9) 22 (6.3) 2 (0.6) 17 (4.9) Moyes [228] 4 275 1 090 434 (10.2) 283 (6.6) 227 (5.3) (25.5) Cohen [242] 8 123 2 061 877 (10.8) 622 (7.7) 504 (6.2) (25.4) Lagare [245] 160 20 (12.5) Ma¨ınassara [247] 788 43 (5.5) 35 (4.4) 8 (1.0) Zash [249] 50 11 (22.0) 2 (4.0) Total 30 271 3 595/19 660 200/705 139/1 724 1 369/16 203 1 729/23 342 400/9 466 99/9 628 21/5 719 16/759 837/15 169 156/2 912 (18.3) (28.4) (8.1) (8.4) (7.4) (4.2) (1.0) (0.4) (2.1) (5.5) (5.4) ADENO = adenovirus; CMV = human cytomegalovirus; COR = human coronavirus; EV = enterovirus; FLU = influenza virus;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; **HBOV = human bocavirus; HMPV = human metapneumovirus;** 32

HSV = herpes simplex virus; PCR = polymerase chain reaction; 163

Table produced using the stargazer package in R [66]. 355 Tab. B.7: African Paediatric Pneumonia Aetiology Studies – Nasopharyngeal Aspirate Virology Results 2 Author Total NP Measles (n, %) PARA (n, %) PARA1 (n, %) PARA2 (n, %) PARA3 PCR (n, %) PARA4 (n, %) PV (n, %) RHINO (n, %) RSV (n, %) Other (n, %) Joosting [97] 2 912 201 (6.9) 157 (5.4) 23 (0.8) Forgie [115] 86 3 (3.5) 5 (5.8) 30 (34.9) 1 (1.2) Forgie [116] 67 4 (6.0) Forgie [118] 221 8 (3.6) 0 (0.0) 15 (6.8) Adegbola [125] 448 4 (0.9) 13 (2.9) 20 (4.5) 8 (1.8) Kamiya [141] 60 5 (8.3) Hussey [155] 162 4 (2.5) 19 (11.7) Zar [166] 243 6 (2.5) Madhi [172] 231 7 (3.0) 12 (5.2) Madhi [173] 116 3 (2.6) 1 (0.9) 1 (0.9) McNally [192] 110 13 (11.8) 11 (10.0) Johnson [196] 122 10 (8.2) 8 (6.6) 18 (14.8) 28 (23.0) Berkley [202] 759 18 (2.4) 10 (1.3) 29 (3.8) 260 (34.3) Morrow [206] 199 8 (4.0) 32 (16.1) O' Callaghan-Gordo 807 3 (0.4) 10 (1.2) 7 (0.9) 11 (1.4) 196 (24.3) 50 (6.2) [210] Continued on next page . . . 356 Tab. B.7, continued from previous page . . . Author Total NP Measles (n,

%) PARA (n, %) PARA1 (n, %) PARA2 (n, %) PARA3 PCR (n, %) PARA4 (n, %) PV (n, %) RHINO (n, %) RSV (n, %) Other (n, %) Cardoso [213] 357 Hammitt [216] 805 72 (8.9) 9 (1.1) 5 (0.6) 47 (5.8) 11 (1.4) 184 (22.9) 213 (26.5) Onyango [219] 2 002 Webb [221] 480 136 (28.3) Cohen [223] 6 338 Feikin [224] 350 2 (0.6) 11 (3.1) 22 (6.3) 2 (0.6) 79 (22.6) Moyes [228] 4 275 90 (2.1) 72 (1.7) 272 (6.4) 1 572 1 157 (36.8) (27.1) Cohen [242] 8 123 161 (2.0) 116 (1.4) 535 (6.6) 3 115 2 216 (38.3) (27.3) Lagare [245] 160 39 (24.4) 9 (5.6) 3 (1.9) 31 (19.4) 21 (13.1) 47 (29.4) 56 (35.0) Ma¨ınassara [247] 788 Zash [249] 50 2 (4.0) 1 (2.0) 3 (6.0) Total 30 271 4/448 (0.9) 354/5 178 303/15 517 235/15 401 968/15 729 43/1 772 2/350 (0.6) 5 120/14 306 4 490/20 427 64/4 020 (6.8) (2.0) (1.5) (6.2) (2.4) (35.8) (22.0) (1.6) PARA = parainfluenza virus; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type** 2; PARA3 = **parainfluenza virus type** 3; PARA4 = **parainfluenza virus type 4;** PV = parechovirus; RHINO = **human** rhinovirus; RSV = **respiratory syncytial virus;** **121**

PCR = polymerase chain reaction; Table produced using the stargazer package in R [66]. 357 C PERCH South Africa Catchment Area This Appendix cross-references to Section 2.1.1 of this thesis, which outlines the characteristics of the South African PERCH site, situated in Regions D and G of the City of Johannesburg. The study catchment area was based on the place of residence of 90% of all paediatric admissions to CHBAH in the year preceding PERCH activities at the site (2010). In 2010, there were 7 053 age-eligible

children admitted to the general Paediatric wards at the **hospital,** **233**

see Table C.1, below. 90% (n=6 267) of the age-eligible paediatric admissions in 2010 resided in the 28 suburbs listed in Table C.2. Map A in Figure C.1 depicts the location of Johannesburg and Soweto in South Africa. Map B in Figure C.1 represents Soweto and its surrounds, with suburbs plotted onto a satellite view of Regions D and G of the City of Johannesburg. Map C in Figure C.2 depicts the information listed in Table C.2. 358 C. PERCH South Africa Catchment Area359 Tab. C.1: Place of residence of 7 053 age-eligible children admitted to the CHBAH Paediatric Wards in 2010 Suburb Number % Suburb Number % Orange Farm 638 9.0 Klipspruit 83 1.2 Diepkloof 601 8.5 Dhlamini 78 1.1 Orlando 559 7.9 Phiri 77 1.1 Meadowlands 447 6.3 Poortje 59 0.8 Lenasia South 360 5.1 Ennerdale 75 1.1 Pimville 338 4.8 Doornkop 68 1.0 Protea Glen 260 3.7 Zondi 60 0.9 Power Park 245 3.5 Molapo 56 0.8 Bram Fischerville 226 3.2 Moletsane 54 0.8 Dobsonville 209 3.0 Eikenhof 49 0.7 Chiawelo 207 2.9 Rockville 48 0.7 Zola 205 2.9 Tladi 42 0.6 Mofolo 187 2.7 Nancefield 39 0.6 Jabavu 186 2.6 Devland 33 0.5 Lawley 176 2.5 Grasmere 32 0.5 Finetown 168 2.4 Williers Farm 32 0.5 Naledi 168 2.4 Klerksdorp 28 0.4 Eldorado Park 158 2.2 Sebokeng 28 0.4 Vlakfontein 143 2.0 Snake Park 27 0.4 Emdeni 125 1.8 Solvo Park 26 0.4 Jabulani 95 1.3 Drieziek 25 0.4 Mapetla 95 1.3 Katlehong 24 0.3 Senaoane 90 1.3 Moroka 20 0.3 Dube 84 1.2 Mzimhlophe 20 0.3 CHBAH = Chris Hani Baragwanath Academic Hospital; Table produced using the stargazer package in R [66]. Map A Map B Fig. C.1: Study Catchment Area C. PERCH South Africa Catchment Area 360 Map A: South Africa, with location of Johannesburg (Jhb) and Soweto; Map B: City of Johannesburg Regions D and G – study catchment area shaded in light red; Chris Hani Baragwanath Academic Hospital; • Primary Health Care Clinics. Map B generated using the ggmap package in R [696]. Tab. C.2: Place of residence of 90% of the age-eligible children admitted to the CHBAH Paediatric Wards in 2010 Suburb Number Proportion Suburb Number Proportion Orange Farm 638 10.2 Lawley 176 2.8 Diepkloof 601 9.6 Finetown 168 2.7 Orlando 559 8.9 Naledi 168 2.7 Meadowlands 447 7.1 Eldorado Park 158 2.5 Lenasia South 360 5.7 Vlakfontein 143 2.3 Pimville 338 5.4 Emdeni 125 2.0 Protea Glen 260 4.1 Jabulani 95 1.5 Power Park 245 3.9 Mapetla 95 1.5 Bram Fischerville 226 3.6 Senaoane 90 1.4 Dobsonville 209 3.3 Dube 84 1.3 Chiawelo 207 3.3 Klipspruit 83 1.3 Zola 205 3.3 Dhlamini 78 1.2 Mofolo 187 3.0 Phiri 77 1.2 Jabavu 186 3.0 Poortje 59 0.9 CHBAH = Chris Hani Baragwanath Academic Hospital; Table produced using the stargazer package in R [66]. Bram Fischerville Dobsonville Protea Glen Lenasia South Map C Meadowlands Orlando West Orlando East Diepkloof Lawley Vlakfontein Ennerdale Finetown Orange Farm 02.55 km Fig. C.2: Suburb of Origin of PERCH Participants Map C: PERCH South Africa catchment area – based on the percentage of paediatric admissions admitted to the

Department of Paediatrics and **Child Health** at **Chris Hani Baragwanath Academic Hospital** **2**

( ) in 2010. D Numerators Used for Pneumonia Incidence Rate Calculations This Appendix applies to Section 2.4.4 of this thesis, and describes the CHBAH Paediatric Admission and Discharge Registry for the PERCH study period, drawing a distinction between PERCH and non-PERCH cases, and pneumonia and non-pneumonia cases. Table D.1 summarises the numerators in each group, stratified by age category and HIV status: • Non-PERCH cases, overall (n=8 007); • Non-PERCH cases with pneumonia (n=3 186); • PERCH cases (n=920); • All children (non-PERCH and PERCH combined: n=8 927), and; • All children with pneumonia (non-PERCH cases with pneumonia and PERCH cases: n=4 106). Table D.2 contains population denominator data (low-, mid- and high-estimates (see Appendix E)) stratified by age category and HIV status, as well as numerator data (for children hospitalised with pneumonia at CHBAH during the PERCH study period). Numerator data are stratified by study year (and combined study years). 363 D. Numerators Used for Pneumonia Incidence Rate Calculations 364 Tab. D.1: Numerator Data for Children

Hospitalised at the CHBAH Paediatric Wards During PERCH Non-PERCH Cases Non-PERCH Cases with Pneumonia PERCH Cases Totala Total with Pneumoniab Age-eligible for PERCH 8 007 3 186 920 8 927 4 106 1 to 5 months 2 960 (37.0) 1 271 (39.9) 458 (49.8) 3 418 (38.3) 1 729 (42.1) Age category 6 to 11 months 1 572 (19.6) 727 (22.8) 226 (24.6) 1 798 (20.1) 953 (23.3) 12 to 23 months 1 588 (19.8) 657 (20.6) 157 (17.1) 1 745 (19.5) 814 (19.8) 24 to 59 months 1 887 (23.6) 531 (16.7) 79 (8.6) 1 966 (22.0) 610 (14.9) HIV+ 697 (8.7) 380 (11.9) 115 (12.5) 812 (9.1) 495 (12.1) HIV Status HIV- 5 496 (68.6) 2 149 (67.5) 805 (87.5) 6 301 (70.6) 2 954 (71.9) Unknown status 1 814 (22.7) 657 (20.6) · · · 1 814 (20.3) 657 (16.0) HIV+ 904 (11.2) 454 (14.2) 115 (12.5) 1 019 (11.4) 569 (13.9) HIV Status (pooled analysis)c HIV- 7 103 (88.7) 2 732 (85.8) 805 (87.5) 7 908 (88.6) 3 537 (86.1)

Continued on next page . . . Tab. D **.1, continued from previous page** **515**

. . . Non-PERCH CasesNon-PERCH Cases with Pneumonia PERCH CasesTotala Total with Pneumoniab HIV-infected Children <12 months 43522583518308 HIV-uninfected Children 12 to 23 months 1999817216115 24 to 59 months 27013115285146 <12 months 4 0971 7736014 6982 374 D. Numerators Used for Pneumonia Incidence Rate Calculations 365 12 to 23 months 1 3895591401 529699 24 to 59 months 1 617400641 681464 a All children age-eligible for PERCH that were hospitalised during the study time frame (17th August 2011 to 31st August 2013); b Inclusive of all PERCH cases (regardless of discharge diagnosis), and all non-PERCH cases with a discharge diagnosis of pneumonia; c The pooled analysis reassigned an HIV status to the HIV-unknown group by assuming that the proportion of positive and negative HIV results were identical to that observed in the group of children with available HIV results;

HIV = human immunodeficiency virus; HIV+ = HIV-infected; HIV- = HIV-uninfected. **61**

Tab. D.2: Numerator and Denominator Data Used to Derive Incidence Rates Population Estimate Children Study Yeara Age Group (months) HIV+ HIV- HEU HIV-unexposed All HIV Proportionb HEU Proportionc Middled 1 to 11 816 22 512 6 089 16 423 23 328 0.03 0.26 PERCH Cases Both Years 49 409 173 236 458 0.11 0.38 Non-PERCH Cases Both Years 137 1 136 484 652 1 273 0.11 0.38 CHBAH Pneumonia Cases Both Years 186 1 545 657 888 1 731 0.11 0.38 Middled 12 to 23 817 22 539 6 096 16 443 23 357 0.03 0.26 PERCH Cases Both Years 34 192 75 117 226 0.15 0.33 Non-PERCH Cases Both Years 88 632 246 384 720 0.12 0.34 CHBAH Pneumonia Cases Both Years 122 824 321 501 946 0.13 0.34 Continued on next page . . . 366 Tab. D.2, continued from previous page . . . Population Estimate Children Study Yeara Age Group (months) HIV+ HIV- HEU HIV-unexposed All HIV Proportionb HEU Proportionc Middled 24 to 59 2 460 67 833 18 346 49 486 70 293 0.03 0.26 PERCH Cases Both Years 32 204 67 137 236 0.14 0.28 Non-PERCH Cases Both Years 229 964 317 647 1 193 0.19 0.27 CHBAH Pneumonia Cases Both Years 261 1 168 384 784 1 429 0.18 0.27 Middled 1 to 59 4 094 112 884 30 531 82 353 116 978 0.03 0.26 PERCH Cases Both Years 115 805 315 490 920 0.12 0.34 Non-PERCH Cases Both Years 454 2 732 1 047 1 683 3 186 0.14 0.33 CHBAH Pneumonia Cases Both Years 569 3 537 1 362 2 173 4 106 0.14 0.33 a Time periods were from 17th August 2011 until 16th August 2012 (year 1 of the study), and from 17th August 2012 until 31st August 2013 (year 2 of the study); b The proportion of children in each row of the Table that were estimated to have been HIV-infected; c The proportion of children in each row of the Table that were estimated to have been HIV-exposed, -uninfected; d Middle = middle population estimate, derived as described in Appendix E.

CHBAH = Chris Hani Baragwanath Academic Hospital; HEU = HIV-exposed, -uninfected; HIV = **human** **136**

immunodeficiency virus type 1; **HIV+ = HIV-infected; HIV- = HIV-uninfected;** **61**

Table produced using the stargazer package in R [66]. 367 E PERCH South Africa Catchment Area Under-5 Population The ASSA2008 Model [479] estimates that 3.6% of South African

children <5 years of age, and 3.5% **of** those residing **in** **854**

Gauteng Province, were HIV-infected in 2012 (Table E.1). This (3.5%) estimate was applied to the PERCH catchment area population denominators [456, 460–474], taking into account the antenatal HIV seroprevalence of 29.6% in 2012 (Table E.2), in order to derive the numbers of HIV-infected,

HIV-uninfected and HEU **children <5 years of age** **109**

residing in the catchment area (Tables E.3 and E.4). There is evidence that the Census 2011 under-5 population denominators may have been under- estimated [697–699]: an indicator of this is that the under-5

population comprises only 5.2% of the City of Johannesburg Region D & G population according to Census 2011 estimates (Table E.4) [460–474], whereas in previous Statistics South Africa estimates, the under-5 age group comprised 9.4% of the City of Johannesburg Region D & G population (see footnote to Table E.3) [456]. The Census 2011 data are invaluable, however, as they make it possible to assign population estimates to the sub-district level which is useful in giving an accurate PERCH catchment area population estimate. 368 E. PERCH South Africa Catchment Area Under-5 Population 369 Tab. E.1: HIV Prevalence in South African and Gauteng Province Under-5 Children: 2012 0-4 years All 0-4 years HIV+0-4 years HIV+ (%) South Africa Girls 2 536 574 91 528 3.6 Boys 2 555 360 92 099 3.6 Total 5 091 934 183 627 3.6 Gauteng Province Girls 468 592 16 620 3.5 Boys 473 466 16 760 3.5 Total 942 058 33 380 3.5 HIV+ = HIV-infected; Table derived from [479]. Tab. E.2: Gauteng, City of Johannesburg & South African Antenatal HIV Sero- prevalence: 2007 to 2013 Year City of Johannesburg (%) Gauteng (%) South Africa (%) 2007 29.9 30.5 29.4 2008 31.1 29.9 29.3 2009 29.0 29.8 29.4 2010 29.6 30.4 30.2 2011 28.9 28.7 29.5 2012 29.6 29.9 29.5 2013 27.3 28.6 29.7 Table derived from [324, 326, 700, 701]. Tab. E.3: City of Johannesburg Regions D and G Under-5 Population Estimates: 2012 Region D Region G Total PERCH Catchmenta HIV+b HIV-HEUc HIV- unexposedd Girls <1 year 11 964 6 025 17 989 16 190 567 15 623 4 226 11 398 Girls ≥1 &<2 years 11 974 6 029 18 003 16 203 567 15 636 4 229 11 407 Girls ≥2 &<5 years 36 017 18 137 54 154 48 739 1 706 47 033 12 721 34 312 Boys <1 year 12 119 6 180 18 299 16 469 576 15 893 4 298 11 594 Boys ≥1 &<2 years 12 139 6 190 18 329 16 496 577 15 919 4 305 11 613 Boys ≥2 &<5 years 36 551 18 638 55 189 49 670 1 738 47 932 12 964 34 968 All Children <1 year 24 083 12 205 36 288 32 659f 1 143 31 516 8 524 22 992 All Children ≥1 &<2 years 24 113 12 219 36 332 32 699f 1 144 31 555 8 534 23 020 All Children ≥2 &<5 years 72 568 36 775 109 343 98 409f 3 444 94 965 25 685 69 280 All Children <5 years 120 764 61 199 181 963 163 767f 5 732 158 035 42 743 115 292 Total Populatione 1 348 147 591 314 1 939 461 1 745 515 1 939 461a PERCH catchment area defined as the area in which 90% of age-eligible paediatric admissions to the study hospital resided in the year prior to PERCH activities in Soweto (see Appendix C); b In 2012, 3.5% of under-5 children in Gauteng Province were estimated to be HIV-infected (Table E.1); c Number of HEU children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), minus the number of HIV-infected children; d Number of HIV-unexposed children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), subtracted from the total number of under-5 children in the catchment area; e Total population is adults and children, combined: children under-5 represent 181 963 , i.e. 9.4% of the total 163 767population; f It is evident that the <1 year, ≥1 &<2 year, and ≥2 &<5 year age groups are distributed in proportions of 0.19942 (i.e., 32 659), 0.19967 (i.e., 32 699 98 409 E. PERCH South Africa Catchment Area Under-5 Population 370163 767) and 0.60091 (i.e., 163 767) within the total under-5 age group; HEU = HIV-exposed, -uninfected; HIV+ = HIV-infected; HIV- = HIV-uninfected; Table derived from [456]. E. PERCH South Africa Catchment Area Under-5 Population 371 Tab. E.4: Census 2011 City of Johannesburg Data: Regions D and G Suburb PERCH Catchment Areaa Total Population Under-5 Boys (%)b Under-5 Girls (%)b All Under-5 (%) Number Under-5 HIV+c HIV- HEUd HIV- unexposede Soweto [460] 1 271 628 5.1 4.9 5.0 63 581 2 225 61 356 16 595 44 761 Lenasia South [461] 37 110 4.5 4.4 4.5 1 651 58 1 593 431 1 162 Lawley [462] 33 136 6.5 5.9 6.2 2 054 72 1 982 536 1 446 Vlakfontein [463] 27 291 6.2 6.0 6.1 1 665 58 1 607 435 1 172 Orange Farm [464] 76 767 5.8 5.7 5.8 4 414 154 4 260 1 153 3 107 Poortjie [465] 11 153 6.0 6.0 6.0 669 23 646 175 471 Catchment Area 1 457 085 5.1 74 035 2 591 71 444 19 323 52 121 Population [460–465] Lakeside [466] 23 503 6.1 5.8 6.0 1 398 49 1 349 365 984 Stretford [467] 61 141 6.0 5.9 6.0 3 638 127 3 511 950 2 561 Drie Ziek [468] 35 622 6.5 6.5 6.5 2 315 81 2 234 604 1 630 Zakariyya Park [469] 6 200 4.4 3.7 4.1 251 9 242 65 177 Lenasia [470] 89 714 4.5 4.5 4.5 4 037 141 3 896 1 054 2 842 Kanana Park [471] 21 005 5.2 5.2 5.2 1 092 38 1 054 285 769 Lehae [472] 13 380 6.4 6.2 6.3 843 30 813 220 593 Ennerdale [473] 71 815 5.4 5.5 5.5 3 914 137 3 777 1 022 2 755 Tshepisong [474] 53 260 6.1 6.0 6.1 3 222 113 3 109 841 2 268 Regions D and G 1 832 725 5.2 94 747 3 316 91 431 24 729 66 702 Population [460–474] Johannesburg [459] 4 434 827 4.9 4.8 4.9 215 089 7 528 207 561 56 138 151 423 a PERCH catchment area defined as the area in which 90% of age-eligible paediatric admissions to the study hospital resided in the year prior to PERCH activities in Soweto (see Appendix C); b Percentage of males/ females that were under-5, as appropriate; c In 2012, 3.5% of under-5 children in Gauteng Province were estimated to be HIV-infected (Table E.1); d Number of HEU children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), minus the number of HIV-infected children; e Number of HIV-unexposed children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), subtracted from the total number of under-5 children in the catchment area; HEU = HIV-exposed, -uninfected; HIV+ = HIV-infected; HIV- = HIV-uninfected; Table produced using the stargazer package in R [66]. E. PERCH South Africa Catchment Area Under-5 Population 372 In order to correct for possible under-count of under-5 population in the Census 2011 estimates, the degree to which the City of Johannesburg Regions D and G under-5 denominators differed between the earlier Statistics South Africa estimates [456] and the Census 2011 estimates [460– 94 747474], i.e. 163 767 was used to adjust the Census 2011 estimates (Table E.5). From Appendix C, it is evident that not all of the Soweto region was considered in the PERCH catchment area, therefore the adjusted Soweto under-5 population estimate was further multiplied by a factor of 0.9, indicating that 90% of the Soweto region was eligible for inclusion in the PERCH catchment area. Adjusted under-5 population estimates for the study catchment area are shown in Table E.5. Aetiology-specific incidence rates of severe- and very severe pneumonia in Soweto are calculated using the lower (n=74 035), middle (n=116 978) and upper (n=163 767) estimates of the PERCH catchment area under-5 population (derived from Tables E.4, E.5, and E.3, respectively)

as enumerated in Table 2.2, Section 2.4.4. Focus on

age groups <1 year, ≥1&<2 **years, and** ≥2 &<5 **years,** **830**

as depicted in Table 2.2, was possible by multiplying the total under-5 population by adjustment factors 0.19942, 0.19967 and 0.60091 (see footnotes to Table E.3 [456]). E. PERCH South Africa Catchment Area Under-5 Population 373 Tab. E.5: Census 2011 City of Johannesburg Data: Regions D and G – Corrected for Under-count of Under-5s Suburb PERCH Catchment Areaa Total Population Under-5 Boys (%)b Under-5 Girls (%)b All Under-5 (%) Number Under-5c HIV+d HIV- HEUe HIV- unexposedf Soweto [460] 1 271 628 7.9 7.7 7.8 98 908 3 462 95 446 25 815 69 631 Lenasia South [461] 37 110 7.7 7.6 7.7 2 854 100 2 754 745 2 009 Lawley [462] 33 136 11.0 10.4 10.7 3 551 124 3 427 927 2 500 Vlakfontein [463] 27 291 10.6 10.4 10.5 2 877 101 2 776 751 2 025 Orange Farm [464] 76 767 9.9 9.8 9.9 7 630 267 7 363 1 991 5 372 Poortjie [465] 11 153 10.4 10.4 10.4 1 157 40 1 117 302 815 Adjusted Catchment Area Populationa 1 457 085 8.0 116 978 4 094 112 884 30 531 82 353 Adjusted Region D & 1 832 725 8.9 163 767 5 732 158 035 42 743 115 292 G Population 94 747a PERCH catchment area defined as the area in which 90% of age-eligible paediatric admissions to the study hospital resided in the year prior to PERCH activities in Soweto (see Appendix C); b Percentage of males/ females that were under-5, as appropriate; c Under-5 numbers corrected for possible under-count in the 2011 census as follows: denominators multiplied by 163 767 , i.e. the population estimate of children under-5 resident in City of Johannesburg Regions D & G (Table E.3) [456] divided by the Census 2011 estimate of children under-5 resident in City of Johannesburg Regions D and G (Table E.4) [460–474], with the Soweto denominator further adjusted to reflect 90% of the number derived by the first adjustment; d In 2012, 3.5% of under-5 children in Gauteng Province were estimated to be HIV-infected (Table E.1); e Number of HEU children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), minus the number of HIV-infected children; f Number of HIV-unexposed children derived from antenatal HIV seroprevalence rate in the City of Johannesburg of 29.6% in 2012 (Table E.2), subtracted from the total number of under-5 children in the catchment area; HEU = HIV-exposed, -uninfected; HIV+ = HIV-infected; HIV- = HIV-uninfected; Table produced using the stargazer package in R [66]. F Ethics Clearance Certificates This Appendix presents University of the Witwatersrand HREC clearance certificates for the studies presented in this thesis. 374 UNfVERSITY OF THE WITWATERSRAND, JOHANNESBURG Division of the Deputy Registrar (Research) KllMANRESEARCH ETHICS COMMITIEE (MEDICAL) Rl4149 Professor Shabir A Madh j CLEARANCE CERTIFICATE Mt0Mt01129 PROJECTThe Pncumonja Etiology Research for Child Health Project (PERCH) INVI!:S'I'IGATORSProfessor Sbabir A Madlu. OF:PARTMENTRespiratory and Meningeal Pathogens Kesearch Unit DATE CONSIDERED 26illi2010 DECISION OF THE COMMITTEE*Approved unco11ditioo:llly Unless otherwise specifted tbis etbical clearance is yaJid for S years and may l>e renewed upon oppliCjdion. 13i01!2011 Cl lo\IRPERSON ,..... // (L aton-Jona) ouicli>lines thr written 'infhrmtocl consenl' altachecJ wh.,re applicable cc: Supervisor: DECLARATION OF INVESTIGATOR($) Tn he complei.ed in duplicaltl antl()Nf: <:<)I'Y relumt<ll tu the Secrelary al Kuom 10004, lOth Floor, Senate House, University. I!We fully Ullderstand lfle comiitions w1det which I amiwe are authorized to catTy out the aboven1eutioned research and 1/we. guarantee to e.nsure compliance with these conditions. Should any departure to be. contemplated tium the research procedure a<; approved 1/we undoJtake to resubmit the prorocol to the Commirtee. I agree toll completion of a vearly prcgs report. PLEASE QUOTE THE PROTOCOL NUMBER IALL ENQUIRIES... 375 !INIYERS!TY OF TilE WITWATf.RS R ANO..IOHANNESBURC nivision of ! he QeoytY R.c!!i1itrdr (J!ese-a b) !UIMAN R ESF.ARCII ETH ICS COM MITI£6 IM F.lliCALl Rl4149 Dr D•vid P Moo'e CLEARAN(L Cf RTIPICATEMllOIU2 PROJECT Tuberculosts lnfe:ttion as a Ptedic:pM!ng Factor for Bac1erial Cornm unity·Acquired 1-'·neumonia I NV ES I IGATORSDr Da\'IC P Mc('lrc Q &fA RTM.Vl'Rer.pir:ttory & Mcni11geal Pa t hogene; Rr..- I init 1)4TF. CONSIDERED DECISION OF TBE COM M fl""li li• fl nk'nthl"f'Y.IS sn£<:jfitd thi> eth1cal cfc:ar:.ncto "o:lid fnr .5 ,..e-a rts eqd m a'r he ren..wal upnn 11oplintinn. Oltl01101 2 I CfiAIRPERSOJ'i ....r. .k \ . t'r rofcs!;nr PE CkaiOJ\-Jones) "'li11KS:ehJ1(fo,. vnint'r. ·lnfurmed consen;_' ah;«.:ilcJ wh 1::: .tp,;L<"ll>.e cc: SupcrJisc.r ·Profes or Shabir Mad hi ·····-·····----·-·--·----···-·-----------------------· ·----------·----- nU : I ABATIOOF' t W r.S1't CATO To be oomp c:tcd ir. duplicnre and ONE COPY returnee to d\e Secr.:tary at Room I 00()4, 10th Floor. Senate Hous.e. Uniw"'Sity. 1/\Vt: fuily un(.!.:I laJld tlle (O""di1i<>ns und• which I nmtwe are authu ri t:d 10 out the flho·,e:mcrt!nnc.C rl!search and Jlwe guarautc«.:" 10 1uw·e c cmplil'lnc:t: with theseondition$. Shooh.l any c!epz.nure to be cont mph'ltod ftom the rest!an.:h v•v-..'o!dulli! .u ;tpprt)\t('d """r.untit.rrnketo re:;ubmit the prcl<lcOI to the' 376 -- Human ReseJrch Ethics Committee (Medical) (rormerJy C orrut&fttct for R94rch on lluuon SubJt>cts (Mcodi::.JI) University of the Witwatersrand, Joh< nnesburg 17 September 2012 Dr David Moore Re!earcl Paedratrician Respiratory & MeningealPathogens Rasearch Unit Chris He; Baragwanath Academrc Hospital Unive;si[y Sent by e·mi:lil:moored@rmoru.co za near Dr Moore RE: ProtocolM120210: 'A Post Mortem lung Biopsy Study to Investigate the Aetiology of Pneumonia in Children (PERCHI Erotoeor Amendment This letter

serves to confirm that the Chairman **of** the **Human** Researc!r **Ethics Committee** **779**

(Medic< !) has rev1ewod ana approved tile following amendments un the abovementioned protocol as detailoo 1n your letters dated 03September and 10 September 2012. • Amendment to Lung BIOPSy sub-Study Protocol • />,pprovalletter from CHBAH Med1caJ lldVisory • HREC (Mt dica)l 2012 • Lu11g BioPSy Sue-Study ICF ersion 1.4, 21 August 2012 • lung Blot>sy Genetics ICF version 'l.2, 10 September 2U12 • MaterialTransfer AgreemfInt Version 1. 0, 28 May 2012 • bSitoapnsdyasrdpOimpeerantsing Proced11res for transport of post-mortem lung Thank you for l>ecp!ng us informed and uPdated. Yours since.mly,) Anrsa

I<esllav Secretary Human Research Ethics Committee (Medical) t---------- 377 G ROC Analysis for Pathogen Density Cut-offs: Raw Data Tabulated in this Appendix are the Youden index-derived thresholds which best discriminated between case and control status using ROC analysis Table G.1. Results are briefly described in Section 4.1.2. 378 G. ROC Analysis for Pathogen Density Cut-offs: Raw Data 379 Tab. G.1: Youden Index-derived Cut-off Densities (log10 copies/mL) which Best Distinguished between Cases with Radiologically-confirmed Pneumonia and Controls Pathogen Specimen CXR+ HIV- HEU HIV- unexp. Exp. unk. HIV+ ADENO NP/OP 4.95 4.88 4.99 4.88 4.88 5.92 BOPE NP/OP 5.61 5.61 5.55 5.58 5.61 5.61 CMV NP/OP 5.42 5.40 4.53 4.98 5.69 5.42 CMV WB 3.34 3.34 2.53 3.33 3.31 2.69 COR229 NP/OP 3.74 3.74 3.74 3.74 3.74 3.74 COR43 NP/OP 7.35 4.67 5.28 7.21 4.67 6.60 COR63 NP/OP 6.71 6.70 6.11 7.22 6.70 6.71 CORHKU NP/OP 8.45 7.62 8.00 4.38 7.62 8.45 CPNEU NP/OP 2.72 2.72 3.57 2.49 2.72 2.72 Continued on next page . . . G. ROC Analysis for Pathogen Density Cut-offs: Raw Data 380 Tab. G.1, continued from previous page . . . Pathogen Specimen CXR+ HIV- HEU HIV- unexp. Exp. unk. HIV+ FLUA NP/OP 5.13 5.13 4.66 4.80 5.13 5.13 FLUB NP/OP 4.14 4.14 4.14 4.10 4.14 4.14 FLUC NP/OP 5.81 5.56 5.56 5.56 5.56 5.81 HBOV NP/OP 6.50 6.53 3.64 6.42 6.53 3.73 HIB NP/OP 4.87 5.53 5.42 6.53 5.53 4.84 HINF NP/OP 6.72 6.54 7.32 6.52 6.45 6.29 HMPV NP/OP 4.20 4.71 3.88 4.68 8.00 3.81 MCAT NP/OP 6.71 7.09 6.91 6.82 6.16 6.58 MPNEU NP/OP 3.78 3.78 3.78 3.78 3.78 3.78 PARA1 NP/OP 4.44 3.73 3.73 3.74 3.73 3.60 PARA2 NP/OP 3.90 5.29 5.29 5.29 5.29 3.22 PARA3 NP/OP 6.65 6.33 6.54 6.38 8.00 5.94 PARA4 NP/OP 7.11 6.02 6.51 4.77 6.02 7.11 Continued on next page . . . G. ROC Analysis for Pathogen Density Cut-offs: Raw Data 381 Tab. G.1, continued from previous page . . . Pathogen Specimen CXR+ HIV- HEU HIV- unexp. Exp. unk. HIV+ PJP NP/OP 4.33 4.32 4.41 4.31 4.32 4.67 PNEU NP/OP 7.09 7.09 7.54 7.06 4.97 6.44 lytA WB 2.29 2.23 2.32 2.13 2.23 2.57 PVEV NP/OP 3.56 3.61 3.80 4.40 3.61 3.86 RHINO NP/OP 3.19 3.67 3.95 4.96 3.18 3.36 RSV NP/OP 6.18 6.19 6.24 6.15 6.19 7.62 SAUR NP/OP 4.57 4.37 4.95 5.81 4.40 6.43 Highlighted numbers are inferred cut-off density levels (see text for derivation of these estimates). ADENO = adenovirus; BOPE = B. pertussis ; CMV = human cytomegalovirus; COR229 =

coronavirus 229E; COR43 = **coronavirus OC43;** COR63 = **coronavirus NL63;** CORHKU = **coronavirus HKU1;** 33

CPNEU = C. pneumoniae ; CXR+ = radiologically-confirmed pneumonia; Exp. unk. = HIV-uninfected, HIV exposure status unknown;

FLUA = influenza A; FLUB = influenza B; FLUC = influenza C; HBOV = **human** 45

bocavirus; HEU = HIV-exposed, -uninfected;

HIB = H. influenzae type b; HINF = **H. influenzae** non **-type** 36

b; HIV =

human immunodeficiency virus type 1; HIV- = HIV-uninfected; 15

HIV+ = HIV-infected; HIV-unexp. = HIV-unexposed; HMPV = human metapneumovirus; MCAT = M. catarrhalis ; MPNEU = M. pneumoniae ; NP/OP = nasopharyngeal-oropharyngeal; PARA1 =

parainfluenza virus type 1; PARA2 = **parainfluenza virus type 2;** PARA3 = **parainfluenza virus type 3;** PARA4 = **parainfluenza virus type 4;** 20

PJP = P. jirovecii ; PNEU = S. pneumoniae ; lytA = pneumolysin; PVEV = parechovirus/ enterovirus; RHINO = human rhinovirus;

ROC = Receiver Operating Characteristic; RSV = respiratory syncytial virus; 872

SAUR = S. aureus ; WB = whole blood; Table produced using the stargazer package in R [66]. G.1Pathogen Kernel Density Plots and ROC Curves The plots depicted in this Section show the kernel density distributions of pathogen log10 density in NP/OP or whole blood specimens, and the

ROC curves used to derive **the** optimal **cut-off** log10 density which **best** 896

discriminated cases from controls. The cut-off densities were derived using the Youden index [503], through leave-one-out cross-validation – a method which has been shown to minimise bias in the determination of test accuracy when Youden's method is applied to studies with small sample sizes (n<200) [504]. Only pathogen density cut-offs derived for adenovirus, CMV (in NP/OP and whole blood), human bocavirus, human rhinovirus, Hib, non-type b H. influenzae, M. catarrhalis, pneumococcus (in NP/OP and whole blood), S. aureus and P. jirovecii in HEU, HIV-uninfected and

HIV-infected children with radiologically-confirmed **pneumonia** at **the** **624**

South African PERCH site are shown herein. These cut-off densities were used in the calculation of aORs for case versus control status, given the presence of each pathogen in densities above the Youden cut-off in NP/OP swabs and whole blood. Fig. G.1: Adenovirus (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Com- munity Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. ADENO = adenovirus; aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here);

CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HIV = human immunodeficiency virus **12**

type

1; HIV+ = HIV- infected; **HIV-** = HIV **-uninfected; HIV-** unexp. = **HIV-** **95**

unexposed; NP/OP = nasopharyngeal- oropharyngeal; Sens = sensitivity; Spec = specificity. Fig. G.2: Human bocavirus (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here); CXR = chest radiograph; HBOV = human bocavirus; HEU = HIV-exposed, -uninfected;

HIV = human immunodeficiency virus type 1; **HIV+ = HIV-infected; HIV- = HIV-uninfected;** **61**

HIV-unexp. = HIV-unexposed; NP/OP = nasopharyngeal-oropharyngeal; Sens = sensitivity; Spec = specificity. Fig. G.3: Human rhinovirus (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave- one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here);

CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HIV = human immunodeficiency virus **12**

type

1; HIV+ = HIV- infected; **HIV-** = HIV **-uninfected; HIV-** unexp. = **HIV-** **95**

unexposed; NP/OP = nasopharyngeal-oropharyngeal; RHINO = human rhinovirus; Sens = sensitivity; Spec = specificity. Fig. G.4: Human cytomegalovirus (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here); CMV = human

cytomegalovirus; CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HIV = human immunodeficiency virus **12**

type

1; HIV+ = HIV- infected; HIV- = HIV -uninfected; HIV- unexp. = HIV- 95

unexposed; NP/OP = nasopharyngeal-oropharyngeal; Sens = sensitivity; Spec = specificity. Fig. G.5: Human cytomegalovirus (Whole Blood) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) whole blood organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here); CMV = human

cytomegalovirus; CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HIV = human immunodeficiency virus 12

type

1; HIV+ = HIV- infected; HIV- = HIV -uninfected; HIV- unexp. = HIV- 95

unexposed; Sens = sensitivity; Spec = specificity; WB = whole blood. Fig. G.6: Pneumocystis jirovecii (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave- one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here);

CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HIV = human immunodeficiency virus 12

type

1; HIV+ = HIV- infected; HIV- = HIV -uninfected; HIV- unexp. = HIV- 95

unexposed; NP/OP = nasopharyngeal-oropharyngeal; PJP = P. jirovecii ; Sens = sensitivity; Spec = specificity. Fig. G.7: Haemophilus influenzae type b (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here); CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HIB = H. influenzae type b;

HIV = human immunodeficiency virus type 1; HIV+ = HIV-infected; HIV- = HIV-uninfected; 61

HIV-unexp. = HIV-unexposed; NP/OP = nasopharyngeal-oropharyngeal; Sens = sensitivity; Spec = specificity. Fig. G.8: Haemophilus influenzae non-type b (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here); CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HINF =H. influenzae non-type b;

HIV = human immunodeficiency virus type 1; HIV+ = HIV-infected; HIV- = HIV-uninfected; 61

HIV-unexp. = HIV-unexposed; NP/OP = nasopharyngeal-oropharyngeal; Sens = sensitivity; Spec = specificity. Fig. G.9: Moraxella catarrhalis (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave- one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here);

CXR = chest radiograph; HEU = HIV-exposed, -uninfected; HIV = human immunodeficiency virus 12

type

unexposed; MCAT = M. catarrhalis ; NP/OP = nasopharyngeal-oropharyngeal; Sens = sensitivity; Spec = specificity. Fig. G.10: Staphylococcus aureus (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave- one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here);

type

unexposed; NP/OP = nasopharyngeal-oropharyngeal; SAUR = S. aureus ; Sens = sensitivity; Spec = specificity. Fig. G.11: Streptococcus pneumoniae (NP/OP) Density Cut-off, Comparing Cases with Radiologic Pneu- monia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) NP/OP organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here);

type

unexposed; NP/OP = nasopharyngeal-oropharyngeal; PNEU = S. pneumoniae ; Sens = sensitivity; Spec = specificity. Fig. G.12: Streptococcus pneumoniae lytA (Whole Blood) Density Cut-off, Comparing Cases with Radi- ologic Pneumonia to Community Controls, Stratified by HIV-Exposure and -Infection Status Left hand panel – kernel density plots of case (light red) and control (grey, hashed) whole blood organism densities. Right hand panel represents Receiver Operator Characteristic curves. Youden cut-off (,) derived using leave-one-out cross-validation. aOR = adjusted odds ratio; AUC = area under the curve (shaded in grey here);

type

unexposed; lytA = pneumolysin; Sens = sensitivity; Spec = specificity; WB =whole blood. H Investigation of Children for Tuberculosis This Appendix relates to Section 6.1 of this thesis, and includes analyses of data which describe the completeness of investigation for tuberculosis in the PERCH cohort. Analyses presented in this Appendix include the interrogation of factors which led to one rather than two IS specimens being submitted for Mtb culture (Table H.1) and factors that led clinicians to submit GA specimens on patients under their care (Table H.2). In addition, an analysis of the characteristics of children diagnosed with either culture-confirmed or clinically diagnosed tuberculosis (as a combined group) versus those without a diagnosis of tuberculosis is presented here (Table H.3). Table H.4 presents the clinical characteristics of 27 children with microbiologically-confirmed PTB in the South African PERCH cohort. 395 Tab. H.1: Factors Associated with Submission of One or Two IS Specimens on PERCH Cases – South African Site Two IS Collected (n=785) (%) One IS Collected (n=55) (%) Univariate aOR

0 to 12.0) (n=785) 5.0 (2.0 to 12.5) (n=55) 0.99 (0.96 to 1.01)0.961 Age category 1 to 5 months 384/785 (48.9) 28/55 (50.9) Ref· · · 6 to 11 months 195/785 (24.8) 12/55 (21.8) 1.18 (0.59 to 2.38)0.978 12 to 23 months 142/785 (18.1) 8/55 (14.5) 1.29 (0.58 to 2.91)0.971 24 to 59 months 64/785 (8.2) 7/55 (12.7) 0.67 (0.28 to 1.59)0.961 H. Investigation of Children for Tuberculosis 396 Sex <12 months 206/785 (26.2) 15/55 (27.3) 1.52 (0.54 to 4.28)0.961 ≥12 months 579/785 (73.8) 40/55 (72.7) Ref· · · Male 427/785 (54.4) 27/55 (49.1) Ref· · · Female358/785 (45.6) 28/55 (50.9) 0.80 (0.46 to 1.38)0.961

Continued on next page . . . Tab. H **.1, continued from previous page**

. . . Two IS Collected (n=785) (%) One IS Collected (n=55) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Clinical History TB Contact 44/784 (5.6) 6/55 (10.9) 0.48 (0.19 to 1.18) 0.740 Fever 501/785 (63.8) 40/55 (72.7) 0.67 (0.36 to 1.24) 0.870 Cough 761/785 (96.9) 53/55 (96.4) 1.27 (0.29 to 5.58) 1.000 Difficulty breathing 733/784 (93.5) 51/55 (92.7) 1.13 (0.39 to 3.26) 1.000 Wheeze 220/783 (28.1) 11/54 (20.4) 1.55 (0.78 to 3.07) 0.870 Weight loss/ inability to gain weight 126/781 (16.1) 10/54 (18.5) 0.88 (0.43 to 1.82) 1.000 Duration of Symptoms (days) (median, IQR) Fever 2 (1 to 3) (n=484) 2 (1 to 3) (n=37) 0.93 (0.80 to 1.09)0.961 Cough 3 (2 to 4) (n=749) 3 (2 to 4) (n=51)1.02 (0.95 to 1.10)0.971 H. Investigation of Children for Tuberculosis 397 Difficulty breathing 2 (1 to 3) (n=710) 2 (1 to 3) (n=48) 1.00 (0.89 to 1.12) 1.000 Wheeze2 (1 to 3) (n=200) 2 (1 to 3) (n=11)1.10 (0.76 to 1.60)0.971 Continued on next page . . . H. Investigation of Children for Tuberculosis 398 Tab. H.1, continued from previous page . . . Two IS Collected One IS Collected Univariate aOR P-valuea Multivariate aOR (n=785) (%) (n=55) (%) (95% CI) (95% CI)b Chronic Symptoms (≥14 days) Fever 3/484 (0.6) 1/37 (2.7) 0.23 (0.02 to 2.29) 0.870 Cough 35/749 (4.7) 1/51 (2.0) 2.39 (0.32 to 17.85) 0.961 Difficulty breathing 9/710 (1.3) 1/48 (2.1) 0.58 (0.07 to 4.72) 0.971 Wheeze 4/200 (2.0) 0/11 (0.0) · · · 1.000 Any of the above 39/775 (5.0) 3/53 (5.7) 0.86 (0.26 to 2.90) 1.000 WAZ WAZ (median, IQR) -0.8 (-2.2 to 0.2) -1.4 (-2.2 to -0.8) 1.15 (0.99 to 1.33) 0.626 (n=780) (n=55) ≥-2 556/780 (71.3) 39/54 (72.2) Ref · · · >-3 to <-2 108/780 (13.8) 6/54 (11.1) 1.27 (0.52 to 3.07) 0.971 ≤-3 116/780 (14.9) 9/54 (16.7) 0.90 (0.43 to 1.92) 1.000 Oxygen saturations at admission (%) 94 (87 to 98) (n=782) 96 (88 to 98) (n=55) 0.99 (0.96 to 1.02) 0.961 (median, IQR) Oxygen saturation category ≤92% 353/782 (45.1) 21/55 (38.2) Ref · · · 93 to 95% 94/782 (12.0) 5/55 (9.1) 1.11 (0.41 to 3.03) 1.000 ≥96% 335/782 (42.8) 29/55 (52.7) 0.69 (0.38 to 1.23) 0.870 Continued on next page . . . H. Investigation of Children for Tuberculosis 399 Tab. H.1, continued from previous page . . . Two IS Collected (n=785) (%) One IS Collected (n=55) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Respiratory rate at admission 60 (51 to 68) (n=772) 58 (48 to 68) (n=53) 1.01 (0.99 to 1.03) 0.961 (breaths/min) (median, IQR) Disease Severity Severe 560/785 (71.3) 37/55 (67.3) Ref · · · Very severe 225/785 (28.7) 18/55 (32.7) 0.81 (0.45 to 1.46) 0.961 Danger Signs Central cyanosis 7/785 (0.9) 2/55 (3.6) 0.24 (0.05 to 1.20) 0.626 Head nodding 195/785 (24.8) 12/55 (21.8) 1.16 (0.59 to 2.25) 1.000 Lethargy 24/785 (3.1) 6/55 (10.9) 0.26 (0.10 to 0.65) 0.080 0.34 (0.12 to 0.99) Multiple or prolonged convulsions 8/782 (1.0) 3/55 (5.5) 0.18 (0.05 to 0.72) 0.201 Unable to feed, or vomiting 24/785 (3.1) 3/55 (5.5) 0.55 (0.16 to 1.90) 0.961 everything Clinical signs on admission Deep breathing 115/783 (14.7) 8/55 (14.5) 1.03 (0.47 to 2.24) 1.000 Grunting 43/781 (5.5) 5/54 (9.3) 0.56 (0.21 to 1.49) 0.894 LCWI 754/785 (96.1) 54/55 (98.2) 0.45 (0.06 to 3.37) 0.961 Nasal flaring 656/785 (83.6) 48/55 (87.3) 0.73 (0.32 to 1.66) 0.961 Stridor 40/782 (5.1) 2/54 (3.7) 1.49 (0.35 to 6.40) 0.971 Continued on next page . . . H. Investigation of Children for Tuberculosis 400 Tab. H.1, continued from previous page . . . Two IS Collected One IS Collected Univariate aOR P-valuea Multivariate aOR (n=785) (%) (n=55) (%) (95% CI) (95% CI)b CXR Normal 238/668 (35.6) 10/48 (20.8) Ref · · · Abnormalc 430/668 (64.4) 38/48 (79.2) 0.48 (0.23 to 0.97) 0.446 HIV-infected 90/785 (11.5) 10/55 (18.2) 0.60 (0.29 to 1.24) 0.870 Positive Mantouxd 57/426 (13.4) 1/23 (4.3) 3.33 (0.44 to 25.37) 0.894 TB medication started on day of 21/780 (2.7) 0/55 (0.0) · · · 1.000 admission On TB medication at day of discharge 98/654 (15.0) 7/46 (15.2) 1.00 (0.43 to 2.31) 1.000 Duration of hospitalisation (days) 6 (4 to 9) (n=785) 6 (2 to 13) (n=54) 1.00 (0.99 to 1.01) 0.971 (median, IQR) Outcome – Death Died in-hospital 8/785 (1.0) 11/55 (20.0) 0.04 (0.01 to 0.10) <0.001 0.05 (0.02 to 0.12) Died before post-discharge follow-up 18/664 (2.7) 11/51 (21.6) 0.10 (0.04 to 0.22) <0.001 assessmente All statistical comparisons are between column two (“Two IS collected”) and column three (“One IS Collected”), and were done by means of logistic regression adjusting for age in months. a P-values adjusted using the Benjamini-Hochberg procedure; b In the multivariate model (derived by backward stepwise logistic regression), odds ratio adjusted according to age (in months), pneumonia danger signs (lethargy) on admission and in-hospital death; c Abnormal CXR includes films with consolidation, other infiltrate, or both; d 479 children had available Mantoux results; e 715 cases had available vital status at the post-discharge follow-up assessment.

aOR = adjusted odds ratio; CXR = chest radiograph; IS = induced sputum; **IQR = interquartile range;**

LCWI = lower chest wall indrawing; Ref = referent;

TB = tuberculosis; WAZ = weight-for-age Z-score;

Table produced using the stargazer package in R [66]. Tab. H.2: Factors Associated with Submission of GA on PERCH Cases – South African Site GA Collected (n=498) (%) GA Not Collected (n=422) (%) Univariate aOR

(95% CI) P- valuea Multivariate **aOR (95% CI)** b **Age** (months) **(median, IQR)** **160**

6.0 (3.0 to 13.0) (n=498) 4.0 (2.0 to 11.0) (n=422) 1.01 (1.00 to 1.02)0.3171.02 (1.00 to 1.05) Age category 1 to 5 months 223/498 (44.8) 235/422 (55.7) Ref· · · 6 to 11 months 140/498 (28.1) 86/422 (20.4) 1.72 (1.24 to 2.38)0.009 12 to 23 months 94/498 (18.9) 63/422 (14.9) 1.57 (1.09 to 2.27)0.054 24 to 59 months 41/498 (8.2) 38/422 (9.0) 1.14 (0.70 to 1.83)0.752 H. Investigation of Children for Tuberculosis 401 Sex <12 months 135/498 (27.1) 101/422 (23.9) 1.01 (0.62 to 1.66)1.000 ≥12 months 363/498 (72.9) 321/422 (76.1) Ref· · · Male 268/498 (53.8) 218/422 (51.7) Ref· · · Female230/498 (46.2) 204/422 (48.3) 0.92 (0.71 to 1.20)0.718 Continued on next page . . . Tab. H.2, continued from previous page . . . GA Collected (n=498) (%) GA Not Collected (n=422) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Clinical History TB Contact 37/497 (7.4) 19/422 (4.5) 1.70 (0.96 to 3.01) 0.144 Fever 344/498 (69.1) 244/422 (57.8) 1.61 (1.23 to 2.12) 0.009 Cough 485/498 (97.4) 404/421 (96.0) 1.52 (0.73 to 3.18) 0.392 Difficulty breathing 458/497 (92.2) 404/422 (95.7) 0.52 (0.29 to 0.93) 0.075 Wheeze 147/496 (29.6) 115/421 (27.3) 1.11 (0.83 to 1.48) 0.675 Weight loss/ inability to gain weight 96/496 (19.4) 56/417 (13.4) 1.50 (1.04 to 2.16) 0.077 1.67 (0.83 to 3.35) Duration of Symptoms (days) (median, IQR) Fever 2 (1 to 3) (n=330) 2 (1 to 3) (n=234) 1.07 (0.97 to 1.17)0.314 Cough 3 (2 to 5) (n=472) 3 (2 to 4) (n=394) 1.05 (1.01 to 1.09)0.054 H. Investigation of Children for Tuberculosis 402 Difficulty breathing 2 (1 to 3) (n=435) 2 (1 to 3) (n=392) 1.08 (1.01 to 1.16)0.054 Wheeze2 (1 to 3) (n=131) 2 (1 to 3) (n=105) 1.06 (0.96 to 1.18)0.381 Continued on next page . . . H. Investigation of Children for Tuberculosis 403 Tab. H.2, continued from previous page . . . GA Collected GA Not Collected Univariate aOR P-valuea Multivariate aOR (n=498) (%) (n=422) (%) (95% CI) (95% CI)b Chronic Symptoms (≥14 days) Fever 3/330 (0.9) 2/234 (0.9) 0.99 (0.16 to 6.05) 1.000 Cough 28/472 (5.9) 10/394 (2.5) 2.45 (1.17 to 5.12) 0.054 2.78 (0.67 to 11.62) Difficulty breathing 8/435 (1.8) 3/392 (0.8) 2.48 (0.65 to 9.44) 0.317 Wheeze 4/131 (3.1) 1/105 (1.0) 3.32 (0.36 to 30.56) 0.407 Any of the above 32/488 (6.6) 12/413 (2.9) 2.37 (1.20 to 4.67) 0.052 WAZ WAZ (median, IQR) -1.0 (-2.3 to -0.0) -0.8 (-2.3 to 0.2) 0.99 (0.92 to 1.06) 0.837 (n=497) (n=417) ≥-2 347/497 (69.8) 294/416 (70.7) Ref · · · >-3 to <-2 75/497 (15.1) 51/416 (12.3) 1.25 (0.84 to 1.84) 0.392 ≤-3 75/497 (15.1) 71/416 (17.1) 0.90 (0.63 to 1.29) 0.718 Oxygen saturations at admission (%) 93 (87 to 98) (n=497) 94 (87 to 98) (n=420) 0.99 (0.98 to 1.01) 0.343 (median, IQR) Oxygen saturation category ≤92% 232/497 (46.7) 182/420 (43.3) Ref · · · 93 to 95% 64/497 (12.9) 44/420 (10.5) 1.14 (0.74 to 1.75) 0.718 ≥96% 201/497 (40.4) 194/420 (46.2) 0.81 (0.61 to 1.07) 0.262 Continued on next page . . . H. Investigation of Children for Tuberculosis 404 Tab. H.2, continued from previous page . . . GA Collected (n=498) (%) GA Not Collected (n=422) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Respiratory rate at admission 60 (52 to 68) (n=492) 60 (49 to 68) (n=409) 1.01 (1.00 to 1.02) 0.343 (breaths/min) (median, IQR) Disease Severity Severe 361/498 (72.5) 261/422 (61.8) Ref · · · Very severe 137/498 (27.5) 161/422 (38.2) 0.62 (0.47 to 0.82) 0.009 Danger Signs Central cyanosis 7/498 (1.4) 11/422 (2.6) 0.53 (0.20 to 1.40) 0.338 Head nodding 118/498 (23.7) 128/422 (30.3) 0.72 (0.54 to 0.97) 0.081 Lethargy 17/498 (3.4) 35/422 (8.3) 0.39 (0.22 to 0.71) 0.014 0.23 (0.07 to 0.74) Multiple or prolonged convulsions 3/496 (0.6) 9/421 (2.1) 0.27 (0.07 to 1.01) 0.121 Unable to feed, or vomiting 12/498 (2.4) 32/422 (7.6) 0.30 (0.15 to 0.59) 0.009 everything Clinical signs on admission Deep breathing 63/496 (12.7) 73/420 (17.4) 0.68 (0.47 to 0.98) 0.099 Grunting 32/494 (6.5) 28/419 (6.7) 0.98 (0.58 to 1.66) 1.000 LCWI 482/498 (96.8) 400/422 (94.8) 1.67 (0.87 to 3.23) 0.261 Nasal flaring 409/498 (82.1) 360/419 (85.9) 0.76 (0.53 to 1.09) 0.262 Stridor 15/494 (3.0) 33/420 (7.9) 0.35 (0.19 to 0.66) 0.009 0.19 (0.06 to 0.58) Continued on next page . . . H. Investigation of Children for Tuberculosis 405 Tab. H.2, continued from previous page . . . GA Collected GA Not Collected Univariate aOR P-valuea Multivariate aOR (n=498) (%) (n=422) (%) (95% CI) (95% CI)b CXR Normal 125/428 (29.2) 133/354 (37.6) Ref · · · Abnormalc 303/428 (70.8) 221/354 (62.4) 1.47 (1.09 to 1.99) 0.051 1.50 (0.91 to 2.47) HIV-infected 80/498 (16.1) 35/422 (8.3) 2.08 (1.36 to 3.17) 0.009 2.62 (1.11 to 6.17) Positive Mantouxd 49/329 (14.9) 9/150 (6.0) 2.78 (1.33 to 5.85) 0.033 3.13 (1.30 to 7.54) TB medication started on day of 7/494 (1.4) 16/421 (3.8) 0.35 (0.14 to 0.85) 0.062 0.05 (0.00 to 0.62) admission On TB medication at day of dischargee 91/409 (22.2) 20/359 (5.6) 4.84 (2.91 to 8.04) <0.001 · · · Duration of hospitalisation (days) 7 (4 to 10) (n=498) 6 (4 to 10) (n=421) 0.99 (0.98 to 1.00) 0.132 0.99 (0.97 to 1.00) (median, IQR) Outcome – Death Died in-hospital 12/498 (2.4) 26/422 (6.2) 0.37 (0.18 to 0.75) 0.030 Died before post-discharge follow-up 16/414 (3.9) 33/371 (8.9) 0.41 (0.22 to 0.76) 0.027 assessmentf All statistical comparisons are between column two (“GA collected”) and column three (“GA Not Collected”), and were done by means of logistic regression adjusting for age in months. a P-values adjusted using the Benjamini-Hochberg procedure; b In the multivariate model (derived by backward stepwise logistic regression), odds ratio adjusted according to age (in months), clinical history (including presence of TB contact, history of fever, difficulty breathing, weight loss/ inability to gain weight, chronic cough, or any chronic symptom), pneumonia severity signs on admission (head nodding,

inability to feed or vomiting everything, multiple or prolonged **convulsions,** and **lethargy),** **197**

pneumonia severity categorisation, clinical signs on admission (stridor, deep breathing), timing of initiation of antituberculosis medications, CXR abnormalities, HIV status, Mantoux response, duration of hospitalisation and in-hospital death; c Abnormal CXR includes films with consolidation, other infiltrate, or both; d 479 children had available Mantoux results; e Child discharged home on antituberculosis treatment was not included in the multivariate model which assessed clinician decision to submit GA on children, as this would have represented a consequence of a clinical suspicion of tuberculosis rather than a cause to investigate accordingly; f 715 cases had available vital status at the post-discharge follow-up assessment. aOR =

adjusted odds ratio; CXR = chest radiograph; GA = gastric aspirate; LCWI = lower chest wall indrawing; Ref = referent;

TB = tuberculosis; WAZ = weight-for-age Z-score; 404

Table produced using the stargazer package in R [66]. Tab. H.3: Factors Associated with Tuberculosis versus a Non-tuberculosis diagnosis in PERCH Cases – South African Site Tuberculosis Diagnosed (Clinically or Microbiologically) (n=146) (%) Not Tuberculosis (n=773) (%) Univariate aOR

(95% CI) P- valuea Multivariate **aOR (95% CI)** b **Age** (months) **(median, IQR)** 160

7.0 (4.0 to 15.0) (n=146) 5.0 (2.0 to 11.0) (n=773) 0.99 (0.83 to 1.18)1.0001.03 (1.01 to 1.05) H. Investigation of Children for Tuberculosis 406 Age category Sex 1 to 5 months 62/146 (42.5) 396/773 (51.2) Ref· · · 6 to 11 months 34/146 (23.3) 191/773 (24.7) · · ·1.000 12 to 23 months 32/146 (21.9) 125/773 (16.2) · · ·1.000 24 to 59 months 18/146 (12.3) 61/773 (7.9) · · ·1.000 <12 months 50/146 (34.2) 186/773 (24.1) · · ·1.000 ≥12 months 96/146 (65.8) 587/773 (75.9) Ref· · · Male 81/146 (55.5) 404/773 (52.3) Ref· · · Female65/146 (44.5) 369/773 (47.7) · · ·1.000 Continued on next page . . . Tab. H.3, continued from previous page . . . Tuberculosis Diagnosed (Clinically or Not Tuberculosis (n=773) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Microbiologically) (n=146) (%) Clinical History TB Contact 15/145 (10.3) 41/773 (5.3) · · · 1.000 Fever 110/146 (75.3) 477/773 (61.7) · · · 1.000 Cough 142/146 (97.3) 746/772 (96.6) · · · 1.000 Difficulty breathing 130/146 (89.0) 731/772 (94.7) · · · 1.000 Wheeze 31/146 (21.2) 231/770 (30.0) · · · 1.000 Weight loss/ inability to gain weight 36/144 (25.0) 116/769 (15.1) 1.74 (1.12 to 2.68) 0.137 Duration of Symptoms (days) (median, IQR) Fever 2 (1 to 3) (n=104) 2 (1 to 3) (n=459) 0.61 (0.40 to 0.94) 0.215 Cough 3 (2 to 4) (n=137) 3 (2 to 4) (n=728) 0.97 (0.85 to 1.11)1.000 H. Investigation of Children for Tuberculosis 407 Difficulty breathing 2 (1 to 3) (n=121) 2 (1 to 3) (n=705) 0.88 (0.72 to 1.07)1.000 Wheeze2 (1 to 3) (n=27)2 (1 to 3) (n=209) 1.03 (0.92 to 1.16)1.000 Continued on next page . . . Tab. H.3, continued from previous page . . . Chronic Symptoms (>=14 days) Tuberculosis Diagnosed (Clinically or Microbiologically) (n=146) (%) Not Tuberculosis (n=773) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b WAZ Fever 2/104 (1.9) 3/459 (0.7) · · ·1.000 Cough 9/137 (6.6) 29/728 (4.0) · · ·1.000 Difficulty breathing 1/121 (0.8) 10/705 (1.4) · · ·1.000 Wheeze1/27 (3.7) 4/209 (1.9) 1.96 (0.21 to 18.45) 1.000 Any of the above11/142 (7.7) 33/758 (4.4) · · ·1.000 WAZ (median, IQR) -1.9 (-2.9 to -0.4) (n=144) -0.8 (-2.2 to 0.1) (n=769) 1.06 (0.37 to 3.06)1.000 H. Investigation of Children for Tuberculosis 408 ≥-281/144 (56.2) 560/769 (72.8) Ref · · · >-3 to <-2 29/144 (20.1) 97/769 (12.6) 2.08 (1.29 to 3.36)0.0363.01 (1.55 to 5.83) ≤-334/144 (23.6) 112/769 (14.6) 2.13 (1.36 to 3.35)0.0194.16 (2.12 to 8.20) Continued on next page . . . Tab. H.3, continued from previous page . . . Tuberculosis Diagnosed (Clinically or Microbiologically) (n=146) (%) Not Tuberculosis (n=773) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Oxygen saturations at admission (%) (median, IQR) 94 (88 to 98) (n=146) 94 (87 to 98) (n=770) 0.89 (0.57 to 1.37)1.000 Oxygen saturation category Respiratory rate at admission (breaths/min) (median, IQR) Disease Severity ≤92e/146 (44.5) 349/770 (45.3) Ref· · · 93-95/146 (11.0) 92/770 (11.9) · · ·1.000 ≥96e/146 (44.5) 329/770 (42.7) · · ·1.000 59 (49 to 66) (n=144) 60 (51 to 68) (n=757) 1.00 (0.98 to 1.01)1.000 Severe99/146 (67.8) 522/773 (67.5) Ref· · · H. Investigation of Children for Tuberculosis 409 Very severe47/146 (32.2) 251/773 (32.5) · · ·1.000 Continued on next page . . . H. Investigation of Children for Tuberculosis 410 Tab. H.3, continued from previous page . . . Tuberculosis Diagnosed (Clinically or Not Tuberculosis (n=773) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Microbiologically) (n=146) (%) Danger Signs Central cyanosis 3/146 (2.1) 15/773 (1.9) · · · 1.000 Head nodding 42/146 (28.8) 204/773 (26.4) · · · 1.000 Lethargy 6/146 (4.1) 46/773 (6.0) · · · 1.000 Multiple or prolonged convulsions 1/146 (0.7) 11/770 (1.4) · · · 1.000 Unable to feed, or vomiting everything 6/146 (4.1) 38/773 (4.9) · · · 1.000 Clinical signs on admission Deep breathing 24/144 (16.7) 112/771 (14.5) · · · 1.000 Grunting 7/144 (4.9) 53/768 (6.9) · · · 1.000 LCWI 140/146 (95.9) 741/773 (95.9) · · · 1.000 Nasal flaring 121/145 (83.4) 647/771 (83.9) · · · 1.000 Stridor 6/144 (4.2) 42/769 (5.5) · · · 1.000 Continued on next page . . . Tuberculosis Diagnosed (Clinically or Not Tuberculosis (n=773) (%) Univariate aOR (95% CI) P-valuea Multivariate aOR (95% CI)b Microbiologically) (n=146) (%) CXR Normal 29/127 (22.8) 229/654 (35.0) Ref · · · Abnormal 98/127 (77.2) 425/654 (65.0) · · · 1.000 HIV-infected 48/146 (32.9) 67/773 (8.7) · · · 1.000 Positive Mantoux 46/111 (41.4) 12/368 (3.3) 22.51 (11.19 to 45.28) <0.001 26.48 (12.72 to 55.14) TB medication started on day of 4/143 (2.8) 19/771 (2.5) · · · 1.000 On TB medication at d ay of discharge 94/127 (74.0) 17/641 (2.7) 109.63 (58.04 to 207.05) <0.001 Duration of hospitalisa tion (days) 7 (5 to 11) (n=146) 6 (4 to 10) (n=773) 1.00 (0.99 to 1.01) 1.000 Tab. H.3, continued from previous page . . . admission (median, IQR) Outcome – Death Died in-hospital 3/146 (2.1) 35/773 (4.5) · · ·1.000 Died before post-discharge follow-up assessment 6/124 (4.8) 43/661 (6.5) 0.72 (0.30 to 1.74) 1.000 H. Investigation of Children for Tuberculosis 411 All statistical comparisons are between column two (“Tuberculosis Diagnosed (Clinically or Microbiologically)”) and column three (“Not Tuberculosis”), and were done by means of logistic regression adjusting for age in months. a P-values adjusted using the Benjamini-Hochberg procedure; b In the multivariate model (derived by backward stepwise logistic regression), odds ratio adjusted according to age (in months), pneumonia clinical history of

weight loss or failure to gain weight, WAZ category **and** 877

Mantoux response; c Abnormal CXR includes films with consolidation, other infiltrate, or both; d 479 children had available Mantoux results; e 715 cases had available vital status at the post-discharge follow-up assessment.

aOR = adjusted odds ratio; CXR = chest radiograph; IS = induced sputum; **IQR = interquartile range;** 330

LCWI = lower chest wall indrawing; Ref = referent;

TB = tuberculosis; WAZ = weight-for-age Z-score; 404

Table produced using the stargazer package in R [66]. Tab. H.4: Summary of

Culture-confirmed Tuberculosis Cases – South African PERCH Cohort 25

1st 2nd 1st 2nd 3rd 1st 2nd 25

IS SamplesGA SamplesETT SamplesBasis

for Diagnosis TB **Case** Sex **HIV Status** Age (months) **Severity** 25

CXR PosGA Only IS Only GA & IS Other Mtb Spec. 1 F Neg 4 V.

severe AC Neg Neg Pos Neg N/ Ra **GA1** 2

2 F Neg 14

Severe Uninterp. Neg Neg Pos Neg Neg GA1 2

3 M Neg 15

Severe Normal Neg Neg Pos Neg Neg GA1 2

4 M Neg 30

Severe AC Neg Neg Pos Neg N/ Rb **GA1** 2

5 M Neg 17 V.

severe Normal Neg Neg Pos GA1 6 F **Neg** 25

3

Severe AC Neg Neg Neg Pos Neg GA2 2

7 M Pos 8 V.

severe AC Neg Neg Neg Pos GA2 25

8 F Neg 13

Severe Normal Neg Neg Neg Pos Neg GA2 2

9 M Neg 2 Severe AC Neg

Neg Pos Pos GA2, GA3 10 M Neg 4 Severe AC Neg Neg N/ Rc Neg Pos GA3 11 F Pos 4 Severe AC Neg Neg Neg N/ Rb Pos GA3 2

Continued on next page . . . 412

1st 2nd 1st 2nd 3rd 1st 2nd 25

IS SamplesGA SamplesETT SamplesBasis

for Diagnosis TB Case Sex HIV Status Age (months) Severity 25

CXR PosGA Only IS Only GA & IS Other Mtb Spec. 12 M Neg 33

Severe Normal Pos Neg Neg Neg Neg IS1 2

13 F Neg 2 V.

severe AC Pos Neg IS1 14 M Neg 7 Severe AC Pos Neg Neg Neg IS1 2

15 M Neg 27 V.

severe Normal Pos Neg IS1 16 M Neg 1 V. severe AC Pos Pos Neg IS1, IS2 2

17 M Neg 1

Severe AC Neg Pos IS2 18 M Neg 15 Severe Normal Neg Pos IS2 19 F Neg 1 Severe Normal Neg Pos IS2 2

Continued on next page . . . 413

1st 2nd 1st 2nd 3rd 1st 2nd 25

IS SamplesGA SamplesETT SamplesBasis

for Diagnosis TB Case Sex HIV Status Age (months) Severity 25

CXR PosGA Only IS Only GA & IS Other Mtb Spec. 20 M Neg 4 V.

severe AC Pos Neg Pos Neg IS1, GA1 2

21 M Neg 8

Severe AC Pos N/ Rd N/ Rd Pos IS1, GA2 22 F Neg 13 Severe AC Pos Neg N/ Ra Pos Pos IS1, GA2, GA3 23 F Neg 1 Severe AC Pos Pos Pos Pos IS1, IS2, GA1, GA2 2

24 F Neg 15

Severe AC Neg Pos Pos Neg Neg Neg IS2, GA1 2

25 F Neg 2 V.

severe AC Pos Neg ETT1 26 M Pos 4 V. severe AC Neg Pos ETT2 27 M Neg 2 Severe AC Neg Neg 2

TBBC AC = airways consolidation; CXR =

chest radiograph; ETT = endotracheal tube; F = female; **GA = gastric aspirate; HIV = human immunodeficiency virus** type 1; **IS = induced sputum;** M = male; **Mtb** = M. **tuberculosis ; Neg = negative; N/R = not resulted; N/** Ra = **specimen leaked**

in transit to the laboratory; N/Rb = Mtb culture not requested, microscopy for acid-fast bacilli was negative; N/Rc = unlabelled specimen, rejected by the laboratory; N/Rd = smear positive for acid-fast bacilli, Mtb culture was not requested; Pos = positive; Spec. = specimen; TBBC = Mtb blood culture; Uninterp. = uninterpretable; V. severe = very severe; Table produced using the stargazer package in R [66]. 414 I Turnitin Similarity Report for this Thesis As mandated by the University, a Turnitin report was generated in order to ascertain originality of this thesis and adherence to good practice in terms of avoiding plagiarism. As the thesis is a large document, and the Turnitin report is 288 pages in length, only the first page of the Turnitin report has been included in this Appendix. According to the report, there was a 22% match between the contents of this thesis and other sources. All of the matches were <1%, however, and when excluding matches larger than 1%, the thesis contents match to other sources was 1%. The full report (as well as the report which excludes all matches <1%) has been included in a compact disc provided to each examiner, on which the PDF copy of this thesis is also contained. 415 ht tjtlr Turnitin Originality Report tb yll!Ol!aJ:!vid'! -lfM!J'oorje llll..ellfJ:OIIII:'-'-Eor...S!Jlllllll.=uj..f"":"Uia.du.""-l!._Sl;"i"-'arity blf Source From Davdi (9101069g) (ca654600-c0f7- 4 b28-9e93- c904e5ef cll56) Pro cessed on 28-Jun-2016 1235 PM SAST ID 979122043 :=:::=:::=:::=:::=:::=::=::::=:::=:::=:::=:::=:::=::=:::=:::=:::=:::=:::=:::=: [!] < 1% m a tch (Int ernet from 07-Apr-2018) http·/@ca demjc p1m com /cjd/artjc!e!E4 /simpl 3/S309f3858?20 [!] < 1% m atch (Int ernet from 07-May-2014) http:/fwww.nesi.be/sites/default /files{JVAC 30 S3_ p df [!] < 1% ma tct1 (Int ernet from 02-Mar<2016) bttp-{ffl"nW jogh om/docl!menh;J'j$$"e201ffi2N!oha! yp! 5 np 2 we h nrjn t p df 0 < 1%matct1 (Int ernet from 29-Aug-2017) http·t!ppen 11d ac zaJbjtstream!lJaoct!ef1J427/11483Abe s!s hsf Xl l O !e ropx d m pdf? seguence-1 0 < 1% matct1 (Int ernet from 26 Feb-2018) hnpsllacactemtc o qp comktct!::uttc! eAJ41sqnpl 3tS1Z9rn5f1224 [!] < 1% matct1 (Int ernet from 03·Jul.:2017) http·ltwwyy ijaspqety pra/ jpde x phpbjas/artjc!ef.:jgw DOZZO/html [!] < 1% match (publications) "Virall nfe ctigns in C t1tldren Vglume I* Spnnger Nature 2017 [!] < 1% matct1 (Int ernet from 10 Jul.:2017) httpslf.ywwnc cctc g oy/el dlpdfs1Yo! 23no7 pdf-version pdf [!] < 1% matct1 (publications) Cohen Cheryl SibonqileWa laza Jocelyn Moyes Michelle Groome StefanoTemoia Marthi Pretgrius Orien ka Hellferscee Halima Dawggd Meeta Chhagan Fat hima Naby Summa ya Haffg ie e Ebrahi m Ya r jaya Kath l een K a hn Stt gil n Nzen z e Ak bona Isbangela Anne yon Gottbem Njco lg Wplter Adam I Cpben B ahatyl Kga koog Mar jgtjm Ve nter and Shah1r A Ma d bl 'F pi rlem jolo gy qf \llrai-Agsocjated Act1te I ower Respi ratory Tr act I nfecti on among Children <5 Years of Age !0 a H jgb HIY preyalence SeWpg Sot db Af pca ?fU9 2Q12 ·" !be Pe d jat r jc lpfgctjpll$ Disease [!£] < 1% matct1 (Int ernet from 1_5 !-pr-2018) bttpsl/acacteW!C O tt p co m /ct dla rt!Cierlj41Stl ppl 3f;) 2691385fl219 [!!] < 1% matct1 (Int ernet from 16 Jul.:2017) bttp·ttreposjtpry 11h o r 11 nllh llstrgamlba n dlef2066f169 266D 6926B pd f?ge gllence-3 [!!] < 1% match (Internet from 07- Apr-2018) htt psl/pneumonai biomedcentra Icom/art ic le sl10.1186/s41479-016-0021-y [!!:] < 1% matct1 (Int ernet from 18 0ct-2017) bttp·llscbolar $110 ac zabJitstreambJandlg/10019 lf96640/e p arsqn improving 2015 pdf? jgAJ iowgd y&ggqugnce 1 < 1% match (Internet fr om 11-Jul-2013) http·//www.ncbin h-1.nih.g ov /pmdartt cles!PMC264 7437I < 1% matct1 (Int ernet from 24-Jan 2016) btt p·/fwww scielosp nm tscielo pbp ?pjd-SfH)42- 96862[!) 800!J5fl001?&sqmt sci arlle)l!&ll n g gs [!!] < 1% match (Int ernet from 10-Jul-2000) http·//www africanthgracic org/9gcsfSafr ca rtf 416