Ambulatory and hospitalized childhood pneumonia: a longitudinal study in a peri-urban low-income community with high vaccination coverage in Sub-Saharan Africa.

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Declaration

I, David le Roux, hereby declare that this thesis is my own work, both in concept and execution, apart from the normal guidance received from my supervisors and contributions by those acknowledged.

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town.

This thesis includes 5 published manuscripts, which are included as literal and word-for-word renditions of the peer-reviewed and published works, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town. I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include these publications. The following manuscripts (all published) are included in the thesis, and are presented as self-contained chapters in the following order:

1) **Childhood pneumonia: a changing spectrum of disease**. le Roux DM, Zar HJ. Pediatric Radiology 2017 Dec;47(13):1855. doi: 10.1007/s00247-017-4010-y.
2) **Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study**. le Roux, DM, Myer, L, Nicol, MP, and Zar, HJ; Lancet Glob Health. 3(2); 95–103. doi: 10.1016/S2214-109X(14)70360-2.
3) **Incidence of childhood pneumonia: facility-based surveillance estimate compared to measured incidence in a South African birth cohort study**. le Roux, DM, Myer, L, Nicol, MP, and Zar, HJ; BMJ Open. 2015 Dec 18;5(12):e009111. doi: 10.1136/bmjopen-2015-009111.
4) **Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors**. le Roux, DM, Myer, L, Nicol, MP, Vanker, A, Stadler JAM, von Delft, E and Zar, HJ. Clinical Infectious Diseases Oct 15, 2019. doi: 10.1093/cid/ciz017
5) **Factors associated with severity of pneumonia among children in a birth cohort in South Africa.** le Roux, DM, Nicol, MP, Vanker, Nduru, PM and Zar, HJ. PLoS ONE 2021: 16(8): e0255790. https://doi.org/10.1371/journal.pone.0255790

As such, each chapter clearly relates to specific thesis objectives and aims, and includes analyses from the same cohort of patients enrolled in the study. Together, they form a body of work that will advance the knowledge and understanding of the incidence, spectrum of disease, severity and

outcomes of childhood pneumonia in this prospective birth cohort. These data are relevant not only for South Africa, but also have broad generalizability to other emerging economies and low- and middle-income countries which are undergoing demographic transition.

My contribution to each of the above manuscripts is outlined in Chapter 1. For all the manuscripts, I was the lead and corresponding author, conducted all analyses and wrote the first drafts. All co-authors read and contributed to the manuscripts; comments were incorporated into the manuscripts prior to submission.

No part of the thesis has been submitted in the past, or is being, or is to be submitted for a degree at this or any other University.

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Abstract

Background

Child pneumonia is a substantial cause of childhood mortality and morbidity; it is the largest single cause of under-5 mortality outside the neonatal period. Incidence of child pneumonia, and pneumonia mortality, have decreased substantially due to improved socio-economic attainment, improved HIV programs, coverage of new conjugate vaccines against *Streptococcus pneumoniae* (PCV) and *Haemophilus influenzae* type B (Hib), access to early antibiotic therapy, and changing prevalence of pneumonia risk factors. Measurement of community-based pneumonia incidence is difficult; risk factors for pneumonia incidence and factors associated with pneumonia mortality are poorly described in low- and middle-income countries. Careful measurement of pneumonia incidence, and prospective analysis of risk factors is necessary to appreciate the evolving complexities of pneumonia causality and mortality. The aim of this work was to describe the incidence and severity of pneumonia in a birth cohort of children in the first 2 years life; and identify risk factors for pneumonia and for severe outcomes.

Methods

A prospective birth cohort, the Drakenstein Child Health Study, enrolled mother-infant pairs in two communities outside Cape Town, South Africa. Pregnant women were recruited and followed through pregnancy, labour and delivery, and the first 2 years of the child's life. Comprehensive data collection of risk factors was done through the first 2 years of life. A community pneumonia surveillance system was established; active case finding was used for birth cohort participants over 4 respiratory seasons. Children were examined at scheduled visits and at the time of pneumonia events.

Pneumonia or severe pneumonia was diagnosed according to revised World Health Organisation (WHO) guidelines. Chest x-rays were classified according to WHO guidelines. Predictors of ambulatory and hospitalized pneumonia were explored with Poisson regression using generalized estimating equations clustered on mother-infant pairs. Factors associated with death or admission to intensive care unit were analysed with prevalence ratios from modified Poisson regression with robust variance estimation.

Findings

From March 2012 to March 2015, 1137 pregnant women were enrolled, delivering 1143 live-born infants. Household environmental tobacco smoke exposure was common: 82% of children were exposed in the first 6 months of life. Maternal HIV infection was common: 249 (22%) of 1143 children were HIV-exposed, but only 2 children became HIV-infected. Coverage of primary series of

hexavalent vaccine, PCV and Hib was excellent (92%). During the study period (2012 to 2017), there were 795 pneumonia episodes (621 (78%) ambulatory, 274 (22%) hospitalised) in the first 2 years of life. Pneumonia incidence was higher in the first year of life (0.51 episodes per child year (e/cy)) and decreased to 0.25 e/cy in the second year. Active case finding in the birth cohort was more accurate than passive surveillance performed at the community clinics; pneumonia incidence measured by passive surveillance was significantly lower (incidence rate ratio 0.72, 95% CI 0.58 – 0.89) compared to active surveillance. Pneumonia mortality was low: 1.7% of hospitalised cases, and 0.35% of all clinical cases. There was marked variability in pneumonia incidence from year to year during the study. Many risk factors for pneumonia did not have fixed effects**,** but had different impacts at different ages, and variable effect on ambulatory and hospitalised pneumonia. In multivariable regression, adjusted incidence rate ratios were calculated for 5 risk factors (age <6 months, male sex, low birth weight (<2500g), maternal smoking, delayed vaccines), which were associated with consistent effects on ambulatory and hospitalised pneumonia. Risk factors for serious outcomes of pneumonia (death or admission to intensive care unit) were identified: age under 2 months, low birth weight and hypoxia.

Conclusion

In this birth cohort, with low socio-economic status but high vaccination coverage, we demonstrated higher-than expected incidence of pneumonia, but very low mortality, with specific risk factors identified. Active surveillance was important for accurate detection of pneumonia. Children born at low birth weight are at increased risk for pneumonia and for serious outcomes. Pulse oximetry to detect hypoxia, and access to oxygen for children with hypoxic pneumonia, should be included in guidelines. These data will have global applicability for estimation of child pneumonia incidence in regions where direct measurement is impossible. These data can be applied to epidemiology and disease-modelling for child health; they will contribute to long-term morbidity follow-up studies; and they will contribute to understanding the constantly-evolving epidemiology of child pneumonia.

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This thesis has been a tremendous journey; I am very grateful to my supervisors, Prof Zar and Prof Nicol, who were so patient with me, and never gave up on me despite periods of slow progress and low productivity.

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Neon-heart, day-glow eyes
A city lit by fireflies
They're advertising in the skies
For people like us (U2)

A long time ago, I wrote about serving the health needs of the children of Africa. This PhD journey has brought me some valuable insights regarding the hazards that threaten the lives and well-being of some of our most vulnerable. As Nelson Mandela said "There can be no keener revelation of a society's soul than the way in which it treats its children." Completing this PhD has been a journey; but there is another, greater and far more important journey that we must undertake; we still have a long way to go. I trust that completing this PhD will enable me to take another step down that road.

> "The King will reply, 'Truly I tell you, whatever you did for one of the least of these brothers and sisters of mine, you did for me." Mat 25:40 (NIV)

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List of abbreviations

aOR	Adjusted odds ratio
ART	Anti retroviral therapy
BCG	Bacille Calmette Guerin
CAP	Community-acquired pneumonia
CCM	Community Case Management
CDC	Centre for Disease Control and Prevention
CHERG	Child Health Epidemiology Reference Group
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous positive airways pressure
CrI	Credible interval
CRP	C-reactive protein
DALY	Disability-adjusted life year
DCHS	Drakenstein Child Health Study
DTP	Diphtheria-Tetanus-Pertussis vaccine
e/cy	Episodes per child year
EBF	Exclusive breast feeding
EPI	Expanded Program of Immunisation
EPIC	Etiology of Pneumonia in the Community
ETS	Environmental tobacco smoke
GBD	Global Burden of Disease
GVAP	Global Vaccine Access Plan
HEU	HIV-exposed uninfected
Hib	*Haemophilus influenzae* type B
HibCV	*Haemophilus influenzae* type B conjugate vaccine
HIC	High income countries
HIV	Human immune-deficiency virus
HREC	Human Research Ethic Committee
HU	HIV-unexposed
ICU	Intensive care unit
IHME	Institute for Health Metrics and Evaluation
IMCI	Integrated Management of Childhood Illness
IPPV	Intermittent Positive Pressure Ventilation
IQR	Inter quartile range

IRR	Incidence rate ratio
LBW	Low birth weight
LCWI	Lower chest wall indrawing
LMIC	Low- and middle-income countries
LRTI	Lower respiratory tract infection
MCEE	Maternal and Child Epidemiology Estimation
NGO	Non-Governmental Organization
NVP	Nevirapine
PAR	Population attributable risk
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PCV7, 10, 13	7, 10, 13 valent Pneumococcal conjugate vaccine
PEP	Primary end point
PEPC	Primary end point consolidation
PERCH	Pneumonia Etiology for Child Health
PHC	Primary health care
PMTCT	Prevention of mother to child transmission
PTD	Pre term delivery
RR	Risk ratio
RSV	Respiratory syncytial virus
SCR	Sub-costal recession
SD	Standard deviation
SES	Socio-economic status
SEV	Summary Exposure Variable
SSA	Sub Saharan Africa
TB	Tuberculosis
U5	Under 5 years
USA	United States of America
UWFA	Underweight for age
WHO	World Health Organisation
ZDV	Zidovudine

Chapter 1

Background and aims

1.1 Background: Understanding the epidemiology of childhood pneumonia

1.1.1 Childhood pneumonia as a priority disease

Pneumonia is one of the leading causes of mortality and morbidity in children, and the largest single cause of under-5 mortality outside the neonatal period. In 2019, there were 45 million episodes of pneumonia in children under-5 years, and 726 000 under-5 child deaths due to pneumonia.[1] However, the incidence of childhood pneumonia and subsequent child deaths are unequally distributed globally. In high income countries (HIC), pneumonia incidence is 44.6 per 1000 children; countries in Sub Saharan Africa (SSA), incidence of pneumonia is 100.6 per 1000 children, more than double the incidence in HIC, which is also much higher than other low- and middle-income countries (LMIC). Pneumonia mortality in HIC is 3.3 per 100 000 children, compared to 199.5 per 100 000 children in SSA, a 60 fold higher mortality rate.[2] In 2019, childhood pneumonia (age 0-9 years) contributed 61.6 million disability-adjusted life years (DALY's), which is 11.6% of the global total 531 million DALY's.[3]

In addition to pneumonia mortality, children who survive have increased risk of chronic sequelae and long-term complications. Accumulating evidence indicates that much of adult pulmonary disease has its origins in early childhood.[4] Two systematic reviews of prospective studies[5,6] have demonstrated that risk of developing major sequelae (restrictive lung disease, obstructive lung disease, bronchiectasis) was 5.5% after an ambulatory pneumonia event, and 13.6% after a hospitalized pneumonia event, with younger children (under 2 years) having higher risk of developing sequelae than older children.

In addition to the economic cost of childhood pneumonia on global health systems, there are substantial individual costs to the family. Indirect medical costs for a child hospitalized with pneumonia could be up to 31% of a family's weekly income in LMIC, while direct medical costs of hospitalization for severe pneumonia could be 27-116% of a family's monthly income.[7] Health service utilization for childhood pneumonia is high: respiratory conditions in children under 5 are the most common reason for accessing outpatient care and the most common reason for inpatient hospitalization.[8]

The ongoing SARS-CoV2 pandemic has had a number of direct and indirect impacts on childhood pneumonia. The direct impacts have been relatively minor: while children are infected with SARS-CoV2 and can develop symptoms, many of the infections are asymptomatic and most symptomatic

cases are mild.[9] Although there have been thousands of childhood infections, direct mortality due to SARS-CoV2 has been low. Two indirect effects of the pandemic on childhood pneumonia have been due firstly to disruption of health services; and secondly to the macro-economic consequences of the pandemic. There was widespread disruption in provision of routine well-child services (vaccination, vitamin A supplementation and deworming), and coverage of these preventative services was dramatically decreased.[10,11] In some regions, vaccinations have been caught up, but in many areas there has been inadequate catch-up activity.[12] The economic impact of the initial lockdowns as well as the subsequent global recession has resulted in increases in household poverty and food insecurity for children.[13-15] One potential positive indirect effect of the pandemic has been increased attention to the priority of global oxygen supply[16] and provision of oxygen saturation monitors.[17]

While "childhood pneumonia" generally refers to all pneumonia cases under 18 years, and some international estimates refer to the full age range, the highest incidence, morbidity and mortality occurs in children under 2 years of age. Thus this thesis will concentrate primarily on younger children.

1.1.2 Changing epidemiology of childhood pneumonia

The global burden of pneumonia in children decreased by 57% between 1990 and 2019;[3] with case fatality rates decreasing from 2.33% to 0.96%.[18] This partly reflects that all-cause child survival has improved dramatically over the last 50 years. Total under-5 child deaths decreased from 16.4 million per year in 1970 to 5 million per year in 2019,[1] which corresponds to decreases in under-5 mortality rate from 142.6 per 1000 live births in 1970,[19] to 37.1 per 1000 live births in 2019.[20] There are several reasons for these dramatic changes in the epidemiology of childhood pneumonia. It is important to appreciate how the prevalence of risk factors for pneumonia has changed over the last 30 years; how the effect of some risk factors may not be consistent across different clinical contexts; and how careful measurement and interpretation of these risk factors is necessary to ensure correct causal modelling of pneumonia.

a. Decreased global prevalence of major pneumonia risk factors

One of the most important reasons for decreased incidence of childhood pneumonia is reduced prevalence of significant risk factors.[21] Historic risk factors for child pneumonia include pre-term birth, low birth weight, malnutrition, household crowding, inadequate breastfeeding and exposure to smoking. The change in pneumonia risk factors has been quantified as a Summary Exposure Value (SEV, a risk-weighted exposure or prevalence for a population). The SEV for household air pollution secondary to solid fuel use decreased by 43% between 1990 and 2016; SEV's for child underweight decreased by 39%; wasting by 18%; and stunting by 32% between 2005 and 2015. The SEV's for

smoking decreased by 29% between 1990 and 2016, and for second-hand smoke by 21%; for lack of access to handwashing facilities by 7.6%, and for non-exclusive breastfeeding decreased by 5.4%.[21] Global exclusive breastfeeding rates at 6 months increased from 24.9% in 1993 to 35.7% in 2013.[22]

Much of the decreased prevalence of childhood pneumonia risk factors may be due to common root causes of decreased poverty. There have been substantial reductions in absolute global poverty over the last 40 years. In sub Saharan Africa, inflation-adjusted gross national income per capita increased from $550 in 2000 to $1540 in 2019; South Asia increased from $445 to $1993.[23,24] Relationship of poverty to child survival is described in an S-shaped curve; greatest gains in child survival have occurred with economic development in middle-income countries.[25] Furthermore, there have been substantial improvements in maternal education over the last 40 years; the mean number of years of schooling for women of reproductive age in developing countries increased from 2.2 years in 1970 to 7.2 years in 2010.[26] In addition to improvements in maternal education decreasing childhood pneumonia mediated through the pathway of increased socio-economic status in LMIC,[26] there is also a direct effect, as low maternal education has been shown as an independent risk factor for severe pneumonia in LMIC.[27]

Another improvement resulting in decreasing childhood pneumonia incidence and mortality has been in reduced numbers of HIV infected infants and children. HIV infected children are at increased risk of pneumonia,[28,29] and pneumonia is the most common cause of death in children with HIV.[30] Since prioritisation of prevention of mother to child transmission (PMTCT) programs, it is estimated that 1.4 million paediatric HIV infections were prevented between 2000 and 2015.[31] Access to maternal and child anti-retroviral therapy (ART) has contributed to substantial decreases in new infections in children (from 450 000 per year in 2001[32] to 150 000 per year in 2019[31]) and HIV-related child deaths (from more than 300 000 per year in 2003[32] to 95 000 in 2019[31]). Improvement in the paediatric HIV epidemic has contributed to global childhood pneumonia incidence and mortality.

b. Impact of vaccines

Expanded coverage of vaccines has had a substantial impact on the incidence and severity of childhood pneumonia. The Expanded Program on Immunization (EPI), launched by the World Health Organization (WHO) in 1974, established the structures around which country strategies, donor funding, and monitoring and evaluation could be based. Although initially only older vaccines were included (measles, diphtheria, pertussis) and global coverage was relatively low, there has been dramatic increase in rollout of child vaccines in the last decade. Coverage of pentavalent vaccine, (containing vaccines against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B (HibCV), and hepatitis B) increased from 39% in 2010 to 81% in 2019, while 3rd dose of diphtheria-tetanus-

pertussis (DTP3) component increased to 85%.[33] Coverage of the 3rd dose of pneumococcal conjugate vaccine (PCV) increased from 1% in 2010 to 48% in 2019; and of the 2nd dose of measles from 56% in 2013 to 71% in 2019.[33,34] The WHO Integrated Global Action Plan for diarrhoea and pneumonia highlights many opportunities to protect, prevent and treat children has been instrumental in focussing efforts to improve vaccine coverage.[35,36]

The impact on childhood pneumonia has been particularly notable since the introduction of conjugate vaccines targeting *Streptococcus pneumoniae* (PCV) and *Haemophilus influenzae* type B (HibCV). The first Hib vaccine was available in USA from 1987, but due to high cost, 3-dose regimen and need for cold chain, rollout to LMIC was delayed until the late 1990's.[37] In a review of 4 randomized control trials and 2 case-control studies of HibCV in high-burden communities, HibCV was associated with 18% decrease in radiological pneumonia.[38] The HibCV rollout was followed by introduction of PCV in 2000. In vaccine efficacy trials in LMICs, PCV reduced radiological pneumonia by 37% in the Gambia,[39] by 25% in South Africa[40] and by 26% in the Philippines.[41] Subsequent observational data have confirmed decreased incidence of pneumonia post PCV introduction in numerous low and middle-income countries. A systematic review in 2016 of outcomes from 6 Latin American countries after introduction of PCV10 or PCV13 reported decreases of 9-38% for hospitalization due to radiological pneumonia; 7-21% for clinical pneumonia; and 56-83% for invasive pneumococcal disease hospitalization.[42] A subsequent meta-analysis of time-series analyses and before-and-after studies included 6 more studies, 4 from Europe and 1 each from USA and Israel. They reported 9% decrease for hospitalization for clinical pneumonia and 24% decrease for radiological pneumonia.[43]

Recent reports post implementation of PCV into routine health systems in Africa have also shown dramatic impact, table 1.1.

For many LMIC, the period of PCV and HibCV introduction has coincided with improvements in health systems, case management, improved social conditions, and decreases of other risk factors for pneumonia; thus not all of the observed decreases are due to the immunological effect of the vaccine. This is well illustrated by the case of Brazil, which had 90% reduction in all-cause pneumonia mortality from 1980 to 2010, the year that PCV was introduced.[44] There was further reduction in mortality from lower respiratory infections, pneumococcal meningitis and diarrheal disease from 2010 to 2017, but no dramatic change in the nationwide rate of decline in the post PCV era.[45] However, when municipalities were stratified by socio-economic status (SES), the most deprived group had a 19% (95% credible interval (CrI) 7-28%) decrease in pneumonia mortality, which was not significant in medium SES group; there was no effect at all in the highest SES group.[44] The accompanying

editorial comments that "PCV seems to be performing in line with expectations in those settings where it is most needed."[46]

c. Case management of pneumonia

Another reason for decrease in high case fatality of pneumonia, and for overall decrease in numbers of childhood pneumonia deaths, was the introduction of case management of pneumonia from the 1990's, under the assumption that most severe pneumonia was due to bacterial infection and that early antibiotic therapy could prevent death. The WHO pneumonia case definition, based on cough, difficulty breathing and respiratory rate, was designed to be very sensitive, to prioritise children who may have pneumonia for early oral or parenteral antibiotics. Early assessment of the impact of case management showed all-cause mortality decreased by 24% in children 0-4 years, and pneumonia-specific mortality decreased by 36%.[47] Access to community case management (CCM) has been widely expanded; by 2015, 59% of the 74 high priority countries, where 98% of child deaths occur, had adopted a national community case management strategy for childhood pneumonia. This has been strongly associated with reduced child mortality; adopting CCM for both pneumonia and diarrhoea contributed to 12% decline in child mortality.[48] More recently, access to peripheral oxygen saturation monitoring and supplemental oxygen therapy has improved; this has also contributed to increase survival.[17]

d. Changing aetiology of childhood pneumonia

Over the last 40 years, there has been an evolution in the understanding of aetiology of childhood pneumonia, and a growing appreciation of the substantial complexity interactions between aetiological agents. Early investigations into aetiology of radiological pneumonia, relying on blood cultures and lung aspirates, cultured high rates of bacteria: 65% in the Gambia[49] and 61% in Papua New Guinea.[50] This was congruent with contemporary evidence that WHO case management of childhood pneumonia with early antibiotic therapy was effective to decrease mortality.[51]

With the advent of molecular diagnostic techniques, as detection of viruses became easier and as vaccines coverage against pneumococcus and Hib became more widespread, many studies have reflected a change in aetiology of childhood pneumonia towards primarily viral or mixed bacterial-viral. The Etiology of Pneumonia in the Community (EPIC) study enrolled children and adolescents with pneumonia between 2010-2012; respiratory syncytial virus, human rhinovirus and human meta-pneumovirus were the predominant pathogens; bacteria were only detected in 15% of children.[52] The multisite Pneumonia Etiology Research for Child Health (PERCH) study of children hospitalized with severe or very severe pneumonia was conducted in 7 countries from 2011 to 2014. Among 1769

children with positive chest radiography, 61% were attributed to viruses, 27% to bacteria, and 6% to tuberculosis.[53]

1.1.3 Challenges with interpretation of studies of pneumonia risk factors

Decreased exposure to risk factors for childhood pneumonia has driven reduced incidence and severity of childhood pneumonia; however, understanding and interpreting these risk factors can be complex. Over the last 4 decades, concomitant with the decreased incidence of childhood pneumonia, there has been an evolution of the understanding and significance of pneumonia risk factors.

a. Cross sectional vs longitudinal studies

Many recent[53-55] and historical[56] pneumonia risk factor studies were cross-sectional, whereby children presenting at health facilities with pneumonia were enrolled, and comparison was made with community or other non-respiratory controls. However, in cross-sectional studies, where risk factors are ascertained at the time of the pneumonia event, there is possibility of recall bias. Parents interviewed about risk factors may not recall certain exposures accurately, or may be reluctant to report certain exposures, like antenatal maternal smoking, illicit substance use or household smoke exposure.[57] Recency bias may occur, where recent exposures may be over-reported relative to historic exposures.[58] It may be difficult to obtain accurate information about perinatal exposures: even gestation age and birth weight may not be readily available at the time of pneumonia hospitalization, especially in LMIC. Some of the pitfalls of cross-sectional studies for risk factor analysis can be overcome using a different study design, that of a longitudinal birth cohort. A major strength of birth cohorts is that information about exposures is collected prospectively: antenatally, at the time of birth, and through early child, before the pneumonia event occurs. This enables accurate information about prenatal exposures and prospective measurement of biomarkers that reflect forms of indoor and environmental air pollution, and exposure to tobacco smoke. In addition, cross-sectional studies may be influenced by factors associated with access to care, and not reflect true population-based risk; whereas a birth cohort with active case finding can measure the population-level risk of pneumonia irrespective of propensity of families to seek care.

b. Varied effects of risk factors across different contexts: birth weight and anthropometry

As the heterogeneity of childhood pneumonia is appreciated, there is increasing acknowledgement that risk factors do not confer the same degree of increased risk for pneumonia, or for pneumonia-associated mortality, across different clinical contexts. A systematic review analysed 19 risk factors

for severe pneumonia from 36 studies; risk factors from low- and middle-income countries were analysed separately from risk factors from high income countries.[27] Despite some variability in the quality of the included studies, and different case definitions of certain risk factors, there were striking differences between meta-estimates calculated from LMIC vs HIC.

Measures of undernutrition were strongly associated with pneumonia in LMIC, with statistically significant adjusted odds ratios (aOR) noted for low weight-for-age (aOR 4.5, 95% CI 2.1 – 8.5) and low height-for-age (aOR 4.8, 95% CI 3.7 – 6.1). However, in HIC, there was no significant association of severe pneumonia with either underweight (aOR 1.2, 95% CI 0.6 – 2.5) or stunting (aOR 1.3, 95% CI 0.5 – 3.4).[27] Lack of exclusive breastfeeding in LMIC was associated with 2.7 times (95% CI 1.7 – 4.4) increased odds of severe pneumonia, compared to non-significant 1.3 times (95% CI 0.2 – 8.4) increased odds in HIC. Similarly, low birth weight was associated with large increased odds of severe pneumonia in LMIC, albeit with wide confidence intervals: (aOR 3.59 (95% CI 0.79 – 16.27), but the point estimate for low birth weight was smaller in HIC (aOR 2.21, 95% CI 1.34 – 3.64). Notwithstanding that even this analysis is an over-simplification, as within HIC and LMIC there would be great heterogeneity of risk profiles and pneumonia outcomes. Simple dichotomisation of complex groups of data can be misleading.

Despite these caveats, however, this simple analysis serves to illustrate that susceptibility to pneumonia is multifactorial and multi-causal; that risk factors do not confer an absolute, fixed quantum of increased risk; but that the magnitude of effect of a particular risk factor depends on the context and environment in which it is acting. The publications included in the systematic review ranged from 2004 to 2012; most of the LMIC analyses were performed in countries with high incidence of pneumonia but before widespread use of PCV. By contrast, most of the HIC data came from countries using PCV, and had low incidence of pneumonia. It is imperative that these known risk factors be re-evaluated post PCV in countries with high pneumonia burden, to understand their relative contributions to the residual burden of disease in LMIC.

c. Effect of HIV exposure is time-period dependent

The variable effect of certain risk factors in different clinical contexts is also well illustrated by the association between HIV exposure and increased risk of pneumonia. Historically, it was noted that HIV-exposed uninfected (HEU) children had increased incidence of respiratory infections.[59,60] HEU children receive lower levels of transplacental antibody compared to HIV-unexposed (HU) children,[61] and also experience transient abnormalities of innate[62] and adaptive immune function.[63] However, HEU children may be further disadvantaged by increased exposure to household infectious diseases, maternal ill health or premature death, and lower rates of breastfeeding compared to HU children.[64,65]

A systematic review of the clinical outcomes of HEU children in sub-Saharan Africa included 26 articles which described differences between HEU and HU children in Africa, 7 of which specifically described pneumonia incidence.[66] In addition to effect of breastfeeding, use of maternal anti-retroviral therapy (ART) also affected the incidence of pneumonia in HEU children. Maternal ART results in improved maternal health and survival, improved placental antibody transfer, and increased breastfeeding. Since universal maternal ART and the promotion of prolonged breastfeeding for HEU children, the impact of HIV exposure on risk of pneumonia has decreased dramatically compared to the 1990's.[67] Further evidence is emerging that duration of antepartum maternal ART, maternal pre-delivery viral load and nadir CD4 count all affect subsequent infectious morbidity in HEU children in the first year of life.[67] Thus the effect of HIV exposure on pneumonia risk has not been constant over the last 30 years and may also vary by age of child; and even in current practice, there is substantial variability in excess risk depending on maternal health and ART regimen.[68] Therefore it is impossible to describe with a single point estimate the excess risk of pneumonia amongst HEU vs HU children, without acknowledging and accounting for the effect of maternal ART and overall health status.

d. Causal modelling of pneumonia

Causal modelling of risk factors in epidemiology has developed from Henle and Koch's "single agent-single disease" paradigm,[69] or a simple linear chain of risk factors, into a more nuanced appreciation of a "web of causation."[70] In this paradigm, upstream determinants of disease may be related, and have overlapping and inter-related causes. Modern approaches to causal modelling require appreciation of complex interactions between upstream risk factors and determinants, and downstream outcomes of health and disease.[71] Certain risk factors (pre-term birth, low birth weight, incomplete breastfeeding) are easily measured, and may sometimes be analysed as if they were directly causal. However, they may themselves be root causes of other downstream factors which are more direct causes. Alternatively they may be caused or influenced by other upstream risk factors which are not so easily quantified or analysed.

For example, pre-term birth is associated with numerous other pneumonia risk factors: some of these are mediators of pneumonia risk (ie they lie in the causal pathway) like low birth weight, anaemia, stunting, and suboptimal breast feeding. Other risk factors are true confounders: they are associated with the exposure, associated with the outcome, and do not fall in the causal pathway – like maternal illness, maternal mental health, intimate partner violence, and substance abuse disorders.[72] In multivariable regression analyses, it would be incorrect to adjust for a mediator or a collider;[73] regression models that included both the upstream determinant (eg maternal mental health) and the mediator (pre-term birth) would incorrectly estimate the relative contributions of both factors in the causal pathway.[73] It is important that studies investigating risk factors present unadjusted risk

estimates; and that if any adjusted models are presented, that the causal modelling be transparent and explicit. Causal relationship are best described with a directed acyclic graph (DAG)[70,74] of causality, as per figure 1.

1.1.4 Challenges with estimating the incidence of childhood pneumonia

a. Estimation of childhood pneumonia: hospitalization and mortality

Estimation of global incidence of childhood pneumonia is challenging; areas with highest childhood pneumonia burden and mortality tend to have poor quality data on pneumonia cases, hospitalizations and deaths.[75] Thus pneumonia cases cannot simply be counted: pneumonia events are modelled based on what limited data are available at national or regional level. There are 2 major global collaborations which routinely estimate pneumonia incidence and mortality, the Maternal and Child Epidemiology Estimation (MCEE) group within the WHO, and the Institute for Health Metrics and Evaluation (IHME), based at the University of Washington in Seattle, which publishes the Global Burden of Disease (GBD) reports. These research groups have historically used different data sources and very different analyses. Previous global under-5 mortality estimates were markedly different, but recent estimates have converged, with IHME/GBD estimating 5.6 million under-5 deaths in 2016, vs 5.4 million by the MCEE.[76] However the estimates for pneumonia incidence and deaths have remained different: the MCEE group estimated 138 million under-5 pneumonia cases in 2015, with an incidence of 0.23 e/cy; the IHME/GBD estimated that in 2016 there were 68 million pneumonia under-5, equivalent to 0.11 e/cy. The MCEE estimated there were 16.4 million under-5 pneumonia hospitalizations, and 900 000 pneumonia deaths,[18] while the IHME/GBD estimated that there were 5.1 million under-5 pneumonia hospitalization and 652 000 pneumonia deaths.[2]

Methodological differences between the research groups may explain apparent discrepant results. For example, the MCEE model calculates country-specific incidence rates by applying measured incidence rates in the region and national-level prevalence of 7 risk factors: malnutrition (weight for age Z score <-2SD), low birth weight, non-exclusive breastfeeding, indoor air pollution, household crowding, incomplete immunisation and HIV infection.[18] The IHME/GBD model on the other hand calculates attributable fractions of 12 different risk factors (stunting, underweight, wasting, handwashing, breastfeeding, second-hand smoking, zinc deficiency, household air pollution, ambient particulate matter pollution, antibiotic treatment, Hib vaccine and pneumococcal vaccine).[2] However, some of the modelling and methods have not been explicitly explained.[75]

Despite using different methodologies[77,78] and some different data inputs, both IHME and MCEE groups agree on broad trends in global pneumonia epidemiology: decreasing incidence of pneumonia; and decreasing numbers of all-cause and pneumonia-specific child deaths. The accompanying editorial of the MCEE report praised the consistency and transparency of the group's methods over 15 years,[79] while the editorial on the IHME/GBD report commented on the "contentious" methodological challenges in this field.[75] Thus each group and methodology is internally consistent, but the two groups estimates, while showing broadly similar trends, do not make for easy comparisons of a single point estimate or a single region at different time points.

What is especially striking, when looking at current pneumonia incidence estimates, is how old and outdated are some of the sources that are used in the models. The latest MCEE estimate incorporated 46 community-based cohort studies that measured pneumonia incidence between 1980 and 2016.[18] But 33 cohorts had completed data collection before 2000; only 1 cohort was actively recruiting participants after the implementation of both PCV and Hib. There was only 1 birth cohort which had detailed information on antenatal exposures (maternal health, smoking, household air pollution), as well as perinatal history and longitudinal follow up through childhood.[18] As the only way to estimate current pneumonia incidence and mortality is by modelling prevalence of risk factors, it is essential to generate contemporary measured prevalence of pneumonia risk factors and subsequent incidence and severity of pneumonia, including ambulatory events, hospitalizations and deaths.

b. Estimation of ambulatory pneumonia

The 2 research groups' estimates of childhood pneumonia mortality (900 000 vs 652 000) are similar, and are within the uncertainty bounds of one another. However, the estimates of annual pneumonia hospitalizations (16.4 million vs 5.1 million) are more divergent; and the difference in the number of ambulatory pneumonia events is striking: 161 million vs 63 million. This is concerning as neither of the groups actually measure ambulatory pneumonia: the case numbers and incidence estimates are derived from the prevalence of risk factors and attributable fractions in different models, and much of the data that informs the models is several decades old. The underlying assumptions regarding the number of presumed ambulatory events for every documented pneumonia hospitalization or death are based on data collected when many risk factors were more prevalent; many children had simultaneous high-dose exposure to multiple risk factors, in the absence of effective pneumonia case management and conjugate vaccines. The epidemiology of childhood pneumonia has changed so much in the last 30 years, that estimates of the number of uncounted ambulatory episodes per observed death are subject to great uncertainty. As ambulatory pneumonia is less well-studied than hospitalized pneumonia, the knowledge gaps in this area are substantial.

c. Annual variation in pneumonia incidence

Incidence of childhood pneumonia is not constant through the year, nor is it constant across pneumonia seasons. Instead, there is predictable variation through the seasons of each year; variations from year to year are less predictable. Annual variability in pneumonia incidence may be affected by the dynamics of viral circulation, as in some years certain viruses circulate more widely. Some viruses like influenza, have annual antigenic changes, which may make them more or less pathogenic from year to year.[80] Seasonal climate changes can affect severity of pneumonia seasons: temperature and weather conditions can affect dynamics of viral replication; unseasonal rain or decreased temperatures can increase viral transmission, by exacerbating indoor crowding. Seasonal weather changes can also reduce the clean water supplies, and further increase risk of pathogen transmission or incidence of pneumonia.[81] For this reason, pneumonia incidence analyses should span several complete pneumonia seasons; pneumonia incidence should be presented separately by age and by pneumonia season. For example, the multi-site EPIC study calculated pneumonia incidence separately for each year of the study:

> 1 July 2010 to 30 June 2011 pneumonia incidence was 16.8 (95% CI 15.6 – 18.0) per 100 000 child/year
>
> 1 July 2011 to 30 June 2012 pneumonia incidence was 14.6 (95% CI 13.5 – 15.7) per 100 000 child-years.[52]

This study was conducted after the 2009 H1N1 influenza pandemic, when the subsequent influenza seasons were comparatively mild; this may have decreased the burden of influenza, as well as other post-influenza bacterial cases, relative to a year when influenza was circulating more widely. Similarly, the PERCH study enrolled pneumonia cases at each site for 24 months to avoid annual seasonality and minimise year-to-year variability. The authors report that the 2 years of enrolment were also low-influenza circulation years, thus their influenza burden may have also been under-estimated.[53] For this reason, pneumonia incidence estimates in a population should be understood to be dynamic and subject to substantial variability from year to year. As far as possible, pneumonia incidence should be measured over several seasons, and the average incidence presented, as well as each season separately.

1.1.5 Factors associated with severe outcomes of childhood pneumonia

The WHO clinical classification of pneumonia changed in 2013 from 4 categories (no pneumonia, pneumonia, severe pneumonia or very severe pneumonia) to 3 categories (no pneumonia, pneumonia

or severe pneumonia).[82] These categories are intended to provide maximum sensitivity to distinguish children with community-acquired pneumonia who require referral to hospital for assessment, from those who can safely be treated as outpatients with oral antibiotics. However, among those hospitalized, WHO "severe pneumonia" does not further identify those at high risk for death or admission to intensive care unit (ICU),[83] or at risk for prolonged hospitalization. Risk stratifying children hospitalized with pneumonia to identify those at highest risk of serious outcomes can inform management, including enhanced monitoring, earlier initiation of supportive therapy, or referral to a higher level of care.

A systematic review identified 56 studies of hospitalized children describing factors associated with serious outcomes of pneumonia.[84] Many of these were conducted in high-income countries or included older children and teenagers, where case fatality is much lower; some were single-site retrospective cases series, or were conducted before widespread use of PCV or Hib. One of the clinical features that was most strongly associated with death or ICU admission was hypoxia. Hypoxia was variably defined as peripheral oxygen saturation of less than 90 or 92%, reduced arterial partial pressure of oxygen, or decreased PF ratio (ratio of partial pressure of oxygen relative to the fraction of inspired oxygen concentration). But however it was quantified, hypoxia was strongly associated with mortality in both low/middle[84-86] and high-income countries.[83] Young age, particularly age under 6 months, was also one of the factors most consistently associated with increased mortality; while tachypnoea, increased effort of breathing and altered mental status were also associated with death or ICU admission.[84]

More recently, the PERCH study published a pneumonia severity score derived from 1802 HIV-uninfected children under-5 years hospitalized with severe or very severe pneumonia, identifying specific clinical features associated with in-hospital mortality.[87] The PERCH severity score identified infants < 1 year, female sex, decreased level of consciousness, fast breathing without observed cough, grunting, hypoxaemia (peripheral oxygen saturation less than 90%), duration of illness more than 3 days, and severe wasting as risk factors for death from pneumonia.[87] The score had a moderate overall predictive accuracy (C statistic 0.76% in a validation data set), but lower predictive accuracy in some age groups (eg age 6-11 months, where mortality was highest); and at some sites, including South Africa, where mortality was lowest. The authors recommended that the PERCH score should be validated with other datasets.

All risk stratification scores are based on clinical signs and radiological features; however, because they are cross-sectional studies, analysis of the child's early exposure history may be limited by recall bias.[57] To our knowledge, there are no pneumonia severity analyses nested within prospective birth cohorts, with detailed information about the early life determinants of disease including maternal

health, perinatal issues, breastfeeding and early environmental or other household exposures. Although detailed early life and antenatal exposures may not be amenable for inclusion in pneumonia severity scores, exploring these is important in understanding which early life exposures not only affect risk of pneumonia, but also place children at risk of serious outcomes.

Identifying risk factors for death or severe pneumonia remains a topic for ongoing research; factors that predispose a child to develop non-severe pneumonia may not be the same as those that predict or correlate with severe or fatal pneumonia. As the relative contribution of viral causes of pneumonia has increased,[53] case fatality of pneumonia has decreased over time;[18] and yet thousands of children still die from pneumonia every year.[2] Thus it is imperative to understand not only the risk factors for all-cause pneumonia, but also the factors that may predispose to severe or fatal pneumonia.

1.1.6 Summary

Over the last 30 years the incidence of childhood pneumonia and number of child deaths due to pneumonia have decreased substantially, yet pneumonia remains one of the largest global health challenges. The epidemiology of childhood pneumonia has undergone such an evolution in terms of aetiology and risk factors (societal-level, biological and personal-behavioural) it is difficult to extrapolate current global pneumonia case and mortality estimates from old data. There are a number of knowledge gaps in our current understanding of incidence, severity and causal modelling of risk factors for childhood pneumonia. Many incidence and risk factors studies were conducted before widespread use of PCV and Hib: historic risk factor inferences need to be confirmed in communities with high coverage of conjugate vaccines. Many incidence and severity studies were cross-sectional, and do not have reliable antenatal and early infant data, or are subject to recall bias; some studies do not cover different seasons, nor do they investigate risk factors comprehensively. There is a paucity of contemporary prospective cohorts where incidence rates of both ambulatory, hospitalized and severe or fatal pneumonia episodes are accurately measured.

1.2 Aims and hypotheses

Aim

The overall aim of this study was to investigate the incidence, severity and risk factors for childhood pneumonia incidence and serious outcomes in a prospective birth cohort in a low-income setting in South Africa.

Hypotheses

The incidence of ambulatory and hospitalized pneumonia in a prospective birth cohort in a low-income setting in South Africa is different to what has been described in high income countries, and different to pre-vaccination studies in low- and middle-income countries; modifiable risk factors for incidence and progression of pneumonia can be identified to aid prevention efforts; children who will benefit from enhanced surveillance or early referral can be identified. Significant associations of pneumonia with maternal smoking status, household crowding, low birth weight and suboptimal breastfeeding is expected.

Specific aims

1) Investigate the incidence, severity and outcomes of ambulatory and hospitalized pneumonia over several seasons in a longitudinal birth cohort.

2) Investigate risk factors for pneumonia, and compare risk factors for ambulatory to hospitalized pneumonia, over time, and in different age groups.

3) Investigate factors associated with progression of pneumonia (serious outcomes of death or ICU admission)

1.3 Research setting

Birth cohort: background, logistics

The Drakenstein Child Health Study (DCHS) is a birth cohort outside Cape Town, South Africa. Detailed description of the cohort is published elsewhere.[88] Pregnant women (20-28 weeks' gestation) attending antenatal care at one of 2 clinics were recruited and followed through pregnancy, delivery and with their children for 2 years. These two clinics serve 2 communities with different cultural profiles, reflecting South Africa's political history of racial segregation. One community was historically restricted to individuals of mixed ancestry (Newman); the other to individuals of black African ancestry (Mbekweni). Both communities are of low socio-economic status with high unemployment and HIV prevalence.

During the course of the birth cohort enrolment, there were changes in South African national HIV prevention of mother to child transmission (PMTCT) guidelines; birth cohort participants followed different guidelines for anti-retroviral therapy and infant feeding depending on which time period they were enrolled, table 1.2.

Childhood vaccinations followed national schedules: Bacille Calmette Guerin (BCG) at birth; 13-valent pneumococcal conjugate vaccine (PCV13) (6 weeks, 14 weeks, 9 months); hexavalent vaccine (including acellular pertussis and Hib) (6, 10, 14 weeks, and 18 months); and measles vaccine (9 and 18 months). HIV-exposed infants were tested with HIV-DNA PCR) between 6 and 10 weeks, and repeated if hospitalized. Repeat testing occurred at 9- and 18-months using age-appropriate tests according to local guidelines. HIV-exposed infants were given co-trimoxazole prophylaxis from 6 weeks until breastfeeding discontinuation.

Study procedures

The primary outcome was pneumonia incidence, with differentiation by severity (WHO-severe or hospitalization). Study staff, based at both clinics and the single regional hospital, performed pneumonia surveillance using active case finding. Pneumonia was diagnosed according to revised WHO guidelines when a child had cough or difficulty breathing, with either lower chest wall indrawing (LCWI) or age-appropriate tachypnoea ($\geq$ 50 breaths/minute if 2-12 months, $\geq$40 breaths/minute if $\geq$12 months).[82] "Severe" pneumonia was diagnosed in children <2 months with tachypnoea $\geq$ 60 breaths/minute or LCWI; or in children of any age with a danger sign (cyanosed, unable to drink, seizures, or decreased level of consciousness).[82] In children with wheezing, pneumonia was not diagnosed if tachypnoea and LCWI resolved following inhaled bronchodilator. Pneumonia events were diagnosed at the hospital or a clinic; severe cases seen at a clinic were referred to the hospital. Indications for hospitalization included hypoxia (oxygen saturation <92% on room air), or poor social circumstances making ambulatory treatment unfeasible. Decision to hospitalize was made by treating clinicians. Events occurring > 14 days following pneumonia were considered new-onset pneumonia.

1.4 Ethical considerations

The study was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC 401/2009 and HREC 651/2013) and by the Western Cape Provincial Health Research committee (HREC 149/2013). Mothers provided written informed consent at enrolment, with annual renewal.

1.5 Description of included publications as chapters

The 5 chapters in this thesis have been previously published in peer-reviewed journals; the text and data are presented here as literal and word-for-word representation of the published articles, except for the tables and figures have been re-numbered for clarity and internal coherence. I was the primary and corresponding author of all the publications.

1) Childhood pneumonia: a changing spectrum of disease[89]

le Roux DM, Zar HJ. Pediatric Radiology 2017 Dec;47(13):1855. doi: 10.1007/s00247-017-4010-y.

Relevance of paper to thesis:

This was a narrative literature review, performed in 2016, of the developments in childhood pneumonia over the last 40 years, and how the aetiology has shifted from largely bacterial to predominantly viral; and how the burden of disease has changed from severe, hospitalized and often-fatal pneumonia, to relatively milder disease, occurring at lower incidence and with decreased case fatality. This review presents the changes in the incidence and severity of childhood pneumonia without detailed interrogation of how the incidence estimates were obtained, or looking at how the effects of pneumonia risk factors have changed over time. Some of these concepts were only more fully elucidated over the course of the research project.

Contribution of student and co-authors:

I performed the literature review and drafted the manuscript. HJZ directed my reading and developed the concepts through discussion and subsequent drafts.

2) Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study[90]

le Roux, DM, Myer, L, Nicol, MP, and Zar, HJ; Lancet Glob Health. 3(2); 95–103. doi: 10.1016/S2214-109X(14)70360-2.

Relevance of paper to thesis:

This was the first pneumonia paper to be published from the Drakenstein Child Health Study, where we described pneumonia in the first year of life in the first 697 children who were born into the cohort at that time. We described 141 pneumonia episodes (86 ambulatory, 55 hospitalized) with an incidence of 0.27 episodes per child year. This was our first estimate of incidence and severity of pneumonia in this cohort, and paved the way for further assessments with a larger sample size and

longer follow up. This was focussed on Specific Aim 1 (Investigate the incidence, severity and outcomes of ambulatory and hospitalized pneumonia over several seasons in a longitudinal birth cohort) and Specific Aim 2 (Investigate risk factors for pneumonia, and compare risk factors for ambulatory to hospitalized pneumonia, over time, and in different age groups).

Contribution of student and co-authors:

At the time I was working full time on the DCHS as the Study Medical Officer. I drafted the Case Report Forms that were used for collecting the structured interviews with the study participants, and I was involved with recruitment and training of study nurses and field workers, and quality control of study procedures. I cleaned and analysed the data with supervision from LM. I interpreted the data and wrote the first draft of the manuscript. HJZ is the principal investigator, and conceived and designed the study, and obtained funding, together with MPN, the lead microbiologist, and LM, who led the epidemiological analyses. HJZ supervised the writing process, requested additional analyses and directed subsequent drafts.

3) Incidence of childhood pneumonia: facility-based surveillance estimate compared to measured incidence in a South African birth cohort study[91]

le Roux, DM, Myer, L, Nicol, MP, and Zar, HJ; BMJ Open. 2015 Dec 18;5(12):e009111. doi: 10.1136/bmjopen-2015-009111.

Relevance of paper to thesis:

This methods paper describes how the pneumonia surveillance system was established in the district, and compares the active case finding of ambulatory and hospitalized pneumonia events in the birth cohort, to the routine health-worker reports of childhood pneumonia statistics that were reported to the Department of Health. The facility-based surveillance detected 30% fewer pneumonia cases than were detected in the birth cohort, which highlights the importance of carefully-monitored birth cohorts for pneumonia incidence calculation. This was focussed on Specific Aim 1 (Investigate the incidence, severity and outcomes of ambulatory and hospitalized pneumonia over several seasons in a longitudinal birth cohort)

Contribution of student and co-authors:

I collected and analysed the data and drafted the manuscript. LM supervised the data analysis; HJZ supervised the writing process; LM and MN requested additional analyses and directed subsequent drafts.

4) Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors[92]

le Roux, DM, Myer, L, Nicol, MP, Vanker, A, Stadler JAM, von Delft, E and Zar, HJ. Clinical Infectious Diseases Oct 15, 2019. doi: 10.1093/cid/ciz017

Relevance of paper to thesis:

This pneumonia incidence paper describes pneumonia events in 1143 children in the first 2 years of life. We included events occurring over 4 pneumonia seasons, and demonstrated a higher incidence of both ambulatory and hospitalized events than had been found in the initial interim analysis. Risk factors for ambulatory and hospitalized pneumonia were male sex, low birth weight, and maternal smoking. Incomplete vaccination was associated with hospitalized pneumonia; infants who were HIV exposed but uninfected had higher incidence of pneumonia in the first 6 months of life compared to HIV unexposed infants. For this analysis, the term "lower respiratory tract infection" is used interchangeably with "pneumonia." This was focussed on Specific Aim 1 (Investigate the incidence, severity and outcomes of ambulatory and hospitalized pneumonia over several seasons in a longitudinal birth cohort) and Specific Aim 2 (Investigate risk factors for pneumonia, and compare risk factors for ambulatory to hospitalized pneumonia, over time, and in different age groups).

Contribution of student and co-authors:

I reported the chest xray findings (with JAM Stadler and EvD); I analysed the data and wrote the manuscript. The co-authors, LM, MN and HZ reviewed the manuscript and added conceptual and intellectual comment. AV added technical input regarding indoor air pollution. All authors read the manuscript prior to submission.

5) Factors associated with severity of pneumonia among children in a birth cohort in South Africa.[93]

le Roux, DM, Nicol, MP, Vanker, Nduru, PM and Zar, HJ. PLoS ONE 2021: 16(8): e0255790. https://doi.org/10.1371/journal.pone.0255790

Relevance of paper to thesis:

In this paper we explored factors that were associated with severe outcomes (death or admission to intensive care unit). In modified Poisson regression, age < 2 months, preterm birth, or hypoxia (oxygen saturation <92%) were significantly associated with serious outcomes. Preterm birth, low birth weight, HIV exposure, stunting, or underweight-for-age (UWFA) were associated with prolonged hospitalization. This was focused on Specific Aim 3 (Investigate factors associated with progression of pneumonia (serious outcomes of death or ICU admission).

Contribution of student and co-authors:

I performed the primary analysis of the data and wrote the manuscript. PN extracted hospital admission data from the database. MN and HZ reviewed the manuscript and added conceptual and intellectual comment. AV added technical input regarding indoor air pollution. All authors read the manuscript prior to submission.

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1.7 Tables and figures

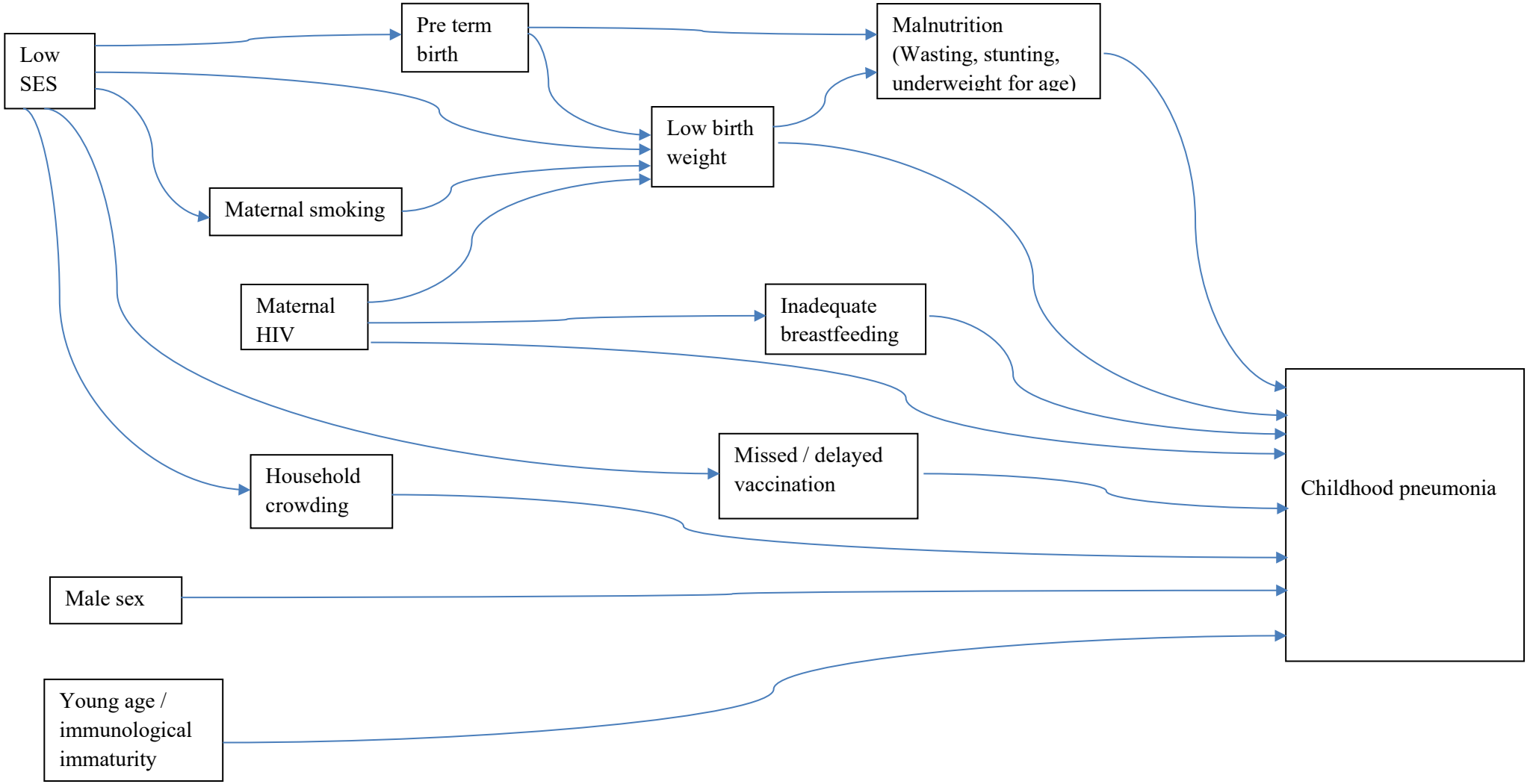
Table 1.1: Child health outcomes after introduction of conjugate vaccines into routine health care services in sub-Saharan Africa

Country	Author (year published)	Outcome	Effect size	Comparator
Malawi	McCollum[94] (2017)	Hypoxic pneumonia Hospitalized pneumonia deaths	Decrease by 47% Decrease by 36%	Post PCV implementation at 75% (compared to pre-PCV)
The Gambia	Mackenzie[95] (2017)	Radiological pneumonia Hypoxic pneumonia	Decrease by 23% in infants 2-22 months Decrease by 29% in children aged 12-23 months Decrease by 57% in infants aged 2-11 months Decrease by 72% in children aged 12-23 months	Pre vs post PCV implementation
South Africa	Von Mollendorf[96] (2017)	Pneumococcal disease in children under 5 years Pneumococcal-related deaths under 5 years	Decrease by 62% Decrease by 63%	Invasive pneumococcal disease pre vs post PCV implementation
Kenya	Silaba[97] (2019)	Clinically-defined pneumonia Radiologically-confirmed pneumonia	Decrease by 27% Decrease by 48%	Pre vs post PCV implementation
Botswana	Congdon[98] (2020)	Pneumonia hospitalizations Pneumonia deaths	Decrease by 48% Decrease by 50%	Pre vs post PCV and Hib introduction

Table 1.2: Maternal antiretroviral and infant prophylaxis regimens in use through the course of the birth cohort

Study period	Maternal antiretroviral therapy	Infant feeding advice
2012 – mid 2013	CD4 count < 350cells/mm^3 or WHO stage 3 or 4 disease: life-long triple antiretroviral therapy (ART) CD4 counts> 350cells/mm^3: zidovudine (ZDV) from 14 weeks gestation, and a single dose of nevirapine (NVP) with 3 hourly ZDV while in labour in labour. (2010 South Africa National HIV Adult and adolescent guidelines)[99]	Free commercial formula milk provided for 6 months (2010 PMTCT guidelines).
Mid 2013 – mid 2015	All HIV-infected women eligible to receive life-long triple ART (2013 South African Antiretroviral Treatment Guidelines)[100]	Women receiving ART encouraged to exclusively breastfeed for 6 months, free formula milk still available
Mid 2015 - 2017	All HIV infected women to urgently commence life-long triple ART on the day that pregnancy was diagnosed (2014 National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults)[101]	All women to breastfeed; free formula milk withdrawn

Figure 1.1 Directed acyclic graph of causes of childhood pneumonia



Chapter 2

Community-acquired pneumonia in children - a changing spectrum of disease

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2.1 Abstract

Pneumonia remains the leading cause of death in children outside the neonatal period, despite advances in prevention and management. Over the last 20 years there have been substantial decreases in the incidence of childhood pneumonia, and in pneumonia-associated mortality. New conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* have contributed to decreases in radiological, clinical and complicated pneumonia cases; and to reduced hospitalization and mortality. The importance of co-infections with multiple pathogens and the predominance of viral-associated disease is emerging. Better access to available, effective preventative and management strategies are needed in low and middle income countries while new strategies are needed to address the residual burden of disease once these have been implemented.

Keywords.

Pneumonia, incidence, epidemiology, radiology, pneumococcal conjugate vaccination

2.2 Introduction

Pneumonia has been the leading cause of death in children under five years of age for decades. Although there have been substantial decreases in overall child mortality and in pneumonia-specific mortality in this time, pneumonia remains the major single cause of death in children outside the neonatal period, causing approximately 900 000 of the estimated 6.3 million child deaths in 2013.[1] Substantial advances have occurred in the understanding of risk factors and etiology of pneumonia, in development of standardized case definitions, in prevention, with production of new, improved vaccines and in treatment. Such advances have led to changes in the epidemiology, etiology and mortality from childhood pneumonia. However, in many areas access and coverage with these interventions remains sub-optimal, with large inequities between and within countries and regions. The aim of this paper is to review the impact of recent preventative or management advances on pneumonia epidemiology, etiology, radiological presentation, and outcome in children.

2.3 Epidemiology and burden of pneumonia in childhood

The overall burden of childhood pneumonia has reduced substantially over the last decade, despite an increase in the global childhood population, from approximately 605 million in 2000 to 664 million in 2015.[2] Recent data suggest that there has been a 25% decrease in the incidence of pneumonia, from 0.29 episodes per child year (e/cy) in low and middle income countries (LMICs) in 2000, to 0.22 e/cy in 2010.[3] This is substantiated by a 58% decrease in pneumonia-associated disability-adjusted life years (DALY's) between 1990 and 2013, from 186 million to 78 million as estimated in the Global Burden of Disease study.[1] Pneumonia deaths decreased from 1.8 million in 2000 to 900 000 per year in 2013.[1] These data do not yet reflect the full impact of increasingly widespread utilization of pneumococcal conjugate vaccine (PCV) in LMICs as the incidence of pneumonia and numbers of deaths is likely to decrease still further with widespread utilization of this intervention.[4]

Notwithstanding this progress, there remains a disproportionate burden of disease in LMICs where over 90% of pneumonia cases and deaths occur. The incidence in high income countries (HIC's) is estimated at 0.015 e/cy, compared to 0.22 e/cy in LMICs.[3]. On average, 1 in 66 children in high income countries may be affected by pneumonia per year, compared to 1 in 5 children in LMICs. Even within LMICs there are regional inequities and challenges with access to health care services: up to 81% of severe pneumonia deaths may occur outside of hospital.[5] In addition to a higher incidence of pneumonia, the case fatality rate is estimated to be almost 10-fold higher in LMICs compared to high income countries.[3,5]

Childhood pneumonia may also lead to significant morbidity and chronic disease. Early life pneumonia may impair long-term lung health by decreasing lung function.[6] Severe or recurrent pneumonia may especially impair lung function; increasing evidence suggests that chronic obstructive pulmonary disease (COPD) may be related to early childhood pneumonia.[7,8] A meta-analysis of the risk of long-term outcomes after childhood pneumonia categorized chronic respiratory sequelae into major (restrictive lung disease, obstructive lung disease, bronchiectasis) or minor (chronic bronchitis, asthma, abnormal pulmonary function).[9] The risk of developing at least 1 of the major sequelae was estimated as 6% after an ambulatory pneumonia event, and 14% after an episode of hospitalized pneumonia. As respiratory diseases affect almost 1 billion people globally, and are a major cause of mortality and morbidity,[10] childhood pneumonia may contribute to substantial morbidity occurring across the life course.

2.4 Changes in presentation of radiological pneumonia

Chest radiological changes have been considered the gold standard for defining a pneumonia event,[11] since clinical findings can be subjective, and clinical definitions of pneumonia may be non-specific. In 2005, to aid in defining outcomes of pneumococcal vaccine studies, the World Health Organization (WHO) "standardized chest X-ray description" was devised to define a group of children who were considered most likely to have pneumococcal pneumonia.[12] "End point consolidation" was described as a dense or fluffy opacity that occupies a portion or whole of a lobe, or of the entire lung. "Other (non-end point) infiltrate" included linear and patchy densities, peribronchial thickening, minor patchy infiltrates that are not of sufficient magnitude to constitute primary end point consolidation, and small areas of atelectasis which in children may be difficult to distinguish from consolidation. "Primary end point (PEP) pneumonia" included either end point consolidation, or a pleural effusion associated with a pulmonary parenchymal infiltrate (including "other" infiltrate).

Widespread use of pneumococcal conjugate vaccination (PCV) and *Haemophilus influenzae* type B conjugate vaccination (HibCV) have decreased the incidence of radiological pneumonia. In a review of 4 randomized control trials and 2 case-control studies of HibCV in high-burden communities, HibCV was associated with 18% decrease in radiological pneumonia.[13] Introduction of PCV was associated with 26% decrease in WHO radiological pneumonia in California between 1995 and 1998.[14] In vaccine efficacy trials in LMICs, PCV reduced radiological pneumonia by 37% in the Gambia [15], by 25% in South Africa [16] and by 26% in the Philippines.[17]

The WHO radiological case definition was not intended to distinguish bacterial from viral etiology, but to define a sub-set of pneumonia cases in which pneumococcal infection was considered more likely; and provide a set of standardized definitions through which researchers could achieve broad

agreement in reporting chest X-rays. However, despite widespread field utilization, there are concerns regarding inter-observer repeatability. There has been good consensus for description of lobar consolidation, but significant disagreement in descriptions of patchy and perihilar infiltrates.[18,19] In addition, many children with clinically severe lung disease do not have "primary end point" pneumonia: in one pre-PCV study, only 34% of children hospitalized with pneumonia had PEP pneumonia.[20] A revised case definition of "presumed bacterial pneumonia" has been introduced which includes pneumonia cases with WHO-defined alveolar consolidation, as well as those with other abnormal chest X-ray infiltrates and a serum C-reactive protein (CRP) of at least 40 mg/L.[21,22] This definition has been shown to have greater sensitivity than the original WHO radiological definition of PEP pneumonia for detecting the burden of pneumonia prevented by PCV.[23] Using this definition, the 10-valent pneumococcal conjugate vaccine, PCV10, had a vaccine efficacy of 22% to prevent presumed bacterial pneumonia in young children in South America,[22] and PCV13 had a vaccine efficacy of 39% in HIV-uninfected children older than 16 weeks in South Africa.[21] Thus there is convincing evidence that PCV decreases the incidence of radiological pneumonia; however, no evidence to suggest that PCV modifies the radiological appearance of pneumococcal pneumonia.

Empyema is a rare complication of pneumonia. An increased incidence in empyema in children was noted in some high-income countries following PCV7 introduction, attributed to pneumococcal serotypes not included in PCV7, especially 3 and 19A.[24] In the USA, evidence from a national hospital database suggested that incidence of empyema increased by 1.9 fold between 1996 and 2008.[25] In Australia, incidence rate ratio was increased by 1.4 times, comparing the pre PCV7 period (1998 to 2004) to the post PCV7 period (2005 to 2010).[26] In Scotland, incidence of empyema in children rose from 6.5 per million between 1981 and 1998, to 66 per million in 2005.[27] These trends have been reversed since the introduction of PCV13. Data from the USA suggest that empyema decreased by 50% in children under 5 years;[28] similarly data from the UK and from Scotland show substantial reductions in pediatric empyema following PCV13 introduction.[29,30]

Several national guidelines from high income countries, as well as the WHO recommendations for LMICs, recommend that chest radiology for children with ambulatory pneumonia should not be performed routinely.[31-33] Indications for chest radiography include hospitalization, severe hypoxemia or respiratory distress, failed initial antibiotic therapy, or if other diseases (tuberculosis, inhaled foreign body) or complications are suspected. However, point of care lung ultrasound is emerging as a promising modality for diagnosis of childhood pneumonia.[34]

2.5 Changes in hospitalization and incidence

In addition to the effect on radiological pneumonia, PCV reduces the risk of hospitalization due to viral-associated pneumonia, probably due to reduced bacterial-viral co-infections resulting in severe disease and hospitalization.[35] An analysis of ecological and observational studies of pneumonia incidence in different age groups soon after introduction of PCV7 in Canada, Italy, Australia, Poland and the USA showed decreases in all-cause pneumonia hospitalizations ranging from 15 to 65%.[36] In the USA after PCV13 replaced PCV7, there was a further 17% decrease in hospitalization for pneumonia among children eligible for vaccination, and a further 12% decrease among unvaccinated adults.[28]

2.6 Changing etiology of childhood pneumonia

A systematic review of etiology studies prior to availability of new conjugate vaccines confirmed *S. pneumoniae* and *H. influenzae* type B (Hib) as the most important bacterial causes of pneumonia, with *Staphylococcus aureus* and *Klebsiella pneumoniae* associated with some severe cases. Respiratory syncytial virus (RSV) was the leading viral cause, identified in 15-40% of pneumonia cases, followed by influenza A and B, parainfluenza, human metapneumovirus and adenovirus.[37]

More recent meta-analyses of etiology data suggest a changing pathogen profile, and increasing recognition that clinical pneumonia is caused by the sequential or concurrent interaction of more than one organism. Severe disease in particular is often due to multiple pathogens. With high coverage of PCV and HibCV vaccination, viral pathogens increasingly predominate.[38] In recent case-control studies, 87% of clinical pneumonia cases in South Africa had at least 1 virus,[39] while viruses were detected in 81% of radiological pneumonia cases in Sweden.[40] In a large multi-center study in the USA, viral pathogens were detected in 73% of children hospitalized with radiological pneumonia, while bacteria were detected in only 15% of cases.[41] A meta-analysis of 23 case-control studies of viral aetiology in radiologically-confirmed pneumonia in children, completed up to 2014, reported good evidence of causal attribution for RSV, influenza, metapneumovirus and parainfluenza virus.[42] However, there was no consistent evidence that many other commonly described viruses, including rhinovirus, adenovirus, bocavirus, and coronavirus, were more commonly isolated from cases than from controls. Further attribution of bacterial aetiology is difficult as it is often not possible to distinguish colonising from pathogenic bacteria when isolated from nasal specimens.[43]

In the last decade there has also been a resurgence in pertussis cases especially in high income countries.[44] As pertussis immunity after acellular pertussis vaccination is less long-lasting than immunity after wild-type infection or whole-cell vaccination, many women of child-bearing age have

waning pertussis antibody levels. Their infants may therefore be born with low transplacental anti-pertussis IgG levels, and are susceptible to pertussis infection before completion of the primary vaccination series.[45] In 2014, more than 40 000 pertussis cases were reported to the Centers for Disease Control and Prevention (CDC) in USA; in some states, population-based incidence rates were higher than at any time in the last 70 years.[44] In contrast, as most LMICs use whole-cell pertussis vaccines, the numbers of pertussis cases has been stable or decreasing until 2015.[46] However, recent evidence from South Africa (where the acellular vaccine is used) shows an appreciable incidence of pertussis among infants under 1 year of age presenting with acute pneumonia: 2% of clinical pneumonia cases among infants enrolled in a birth cohort were due to pertussis;[39] and 3.7% of infants and young children presenting to a tertiary academic hospital had evidence of pertussis infection.[47]

Childhood tuberculosis (TB) is a major cause of morbidity and mortality in many LMICs. *Mycobacterium tuberculosis* has increasingly been recognized as a pathogen in acute pneumonia in children living in high TB-prevalence settings. Post mortem studies of children dying from acute respiratory illness have commonly reported *M. tuberculosis*.[48,49] A recent systematic review of tuberculosis as a comorbidity of childhood pneumonia reported culture-confirmed disease in around 8% of cases.[50] As intrathoracic tuberculosis disease is only culture-confirmed in a minority of cases, the true burden may be even higher than this; tuberculosis may be an important contributor to childhood pneumonia incidence and mortality in high-prevalence areas.

2.7 Changing risk factors for childhood pneumonia

Childhood pneumonia and clinically severe disease results from a complex interaction of host and environmental risk factors.[37] Due to the effectiveness of PCV and HibCV for prevention of radiological and clinical pneumonia, incomplete or inadequate vaccination must be considered as a major preventable risk factor for childhood pneumonia. Other risk factors include low birth weight, which is associated with 3.2 times increased odds of severe pneumonia in LMICs, and 1.8 times increased odds in HIC.[51] Similarly, lack of exclusive breastfeeding for the first 4 months of life increased odds of severe pneumonia by 2.7 in LMIC and 1.3 in HIC. Markers of undernutrition were strong risk factors for pneumonia in LMICs only, with highly significant odds ratios for underweight for age (4.5), stunting (2.6) and wasting (2.8). Household crowding had uniform risk, with odds ratios between 1.9 and 2.3 in both LMIC and HIC. Indoor air pollution, due to use of solid or biomass fuels, increased odds of pneumonia by 1.6 times; lack of measles vaccination by the end of the first year of life increased odds of pneumonia by 1.8 times.[51] It is estimated that the prevalence of these critical risk factors in LMICs has decreased by 25% between 2000 and 2010, contributing to reductions in pneumonia incidence and mortality in LMICs, even in countries where conjugate vaccines have not been available.[3]

HIV infection, especially prevalent in children in sub-Saharan Africa, is the single strongest risk factor for pneumonia. HIV-infected children have 6 times increased odds of developing severe pneumonia or of death compared to HIV-uninfected children.[52] Due to effective prevention of mother-to-child transmission of HIV, there is a growing population of HIV exposed-uninfected (HEU) children; their excess risk of pneumonia, compared to HIV unexposed children, has been described as 1.3 to 3.4 fold higher.[53-57]

2.8 Prevention strategies: new advances

Vaccination with PCV and HibCV have been effective tools to decrease pneumonia incidence, severity and mortality.[58,59] However, coverage and equity of access to vaccines remains sub-optimal. By the end of 2015, HibCV had been introduced in 73 countries, with global coverage estimated at 68%. However, inequities are still apparent between regions; in the Americas, coverage is estimated at 90%, while it is only 25% in the Western Pacific. By 2015, PCV had been introduced into 54 countries, with global coverage of 35% for 3 doses of PCV for infant populations .[60] The Global Vaccine Access Plan is an ambitious WHO initiative to make life-saving vaccines more equitably available. In addition to securing guarantees for financing of vaccines, the program objectives include building political will in LMICs to commit to immunisation as a priority; social marketing to individuals and communities; strengthening health systems; and promoting relevant local research and development innovations.[61]

Maternal vaccination to prevent disease in infants in the first few months of life, has been shown to be effective for tetanus, influenza and pertussis.[62] Influenza vaccination during pregnancy is safe, provides reasonable maternal protection against influenza, and also protects infants for a limited period from confirmed influenza infection (vaccine efficacy 63% in Bangladesh[63] and 50.4% in South Africa.)[64] However, as antibody levels dropped sharply after birth, infant protection did not persist much beyond 8 weeks.[65] Recently, RSV vaccination in pregnancy has been shown to be safe and immunogenic, and a phase 3 clinical trial of efficacy at preventing RSV disease in infants is under way.[66] It is possible that within a decade RSV in infancy may be vaccine preventable, with further decreases in pneumonia incidence, morbidity and mortality.[67]

Improved access to health care, better nutrition and improved living conditions may contribute to further decreases in childhood pneumonia burden. The WHO Integrated Global Action Plan for diarrhea and pneumonia highlights many opportunities to protect, prevent and treat children.[68] Breastfeeding rates can be improved by programs that combine education and counseling interventions in homes, communities and health facilities, and promotion of baby-friendly hospitals.[69]

Improved home ventilation, cleaner cooking fuels and reduction in exposure to cigarette smoke are essential interventions to reduce the incidence and severity of pneumonia.[70,71] Prevention of pediatric HIV is possible, by providing interventions to prevent mother to child transmission.[72] Early infant HIV testing and early initiation of antiretroviral therapy and cotrimoxazole prophylaxis can substantially reduce the incidence of community-acquired pneumonia among HIV-infected children.[73] Community-based interventions reduce pneumonia mortality, and have an indirect effect of improved care seeking behavior.[58] If these available, cost-effective interventions were scaled up, 67% of pneumonia deaths in LMICs could be prevented by 2025.[58]

2.9 Management: recent advances

Case management of pneumonia is a strategy by which severity of disease is classified as severe or non-severe. All children receive early, appropriate oral antibiotics, and severe cases are referred for parenteral antibiotics. When implemented in high-burden areas before the availability of conjugate vaccines, case management as part of Integrated Management of Childhood Illness (IMCI) was associated with 27% decrease in overall child mortality, and 42% decrease in pneumonia-specific mortality.[74] However, the predominance of viral causes of pneumonia and low case fatality has prompted concern about overuse of antibiotics. Several randomized controlled trials comparing oral antibiotics to placebo for non-severe pneumonia have been performed [75-77] and others are ongoing.[78] In two studies, performed in Denmark and in India, outcomes of antibiotic and placebo treatments were equivalent.[76,77] In the third study, in Pakistan, there was a non-significant 24% vs 20% rate of failure in the placebo group, which was deemed to be non-equivalent to the antibiotic group.[75] Furthermore, as WHO non-severe pneumonia and bronchiolitis may be considered a spectrum of lower respiratory disease, many children with clinical pneumonia may actually have viral bronchiolitis, for which antibiotics are not beneficial.[79]

This has been reflected in British[33] and Spanish[31] national pneumonia guidelines, which do not recommend routine antibiotic treatment for children under 2 years with evidence of PCV vaccination who present with non-severe pneumonia. The US national guidelines recommend withholding antibiotics in children up to age 5 years presenting with non-severe pneumonia.[32] However, given the high mortality from pneumonia in LMICs, the lack of easy access to care and the high prevalence of risk factors for severe disease, revised WHO pneumonia guidelines still recommend antibiotic treatment for all children who meet the WHO pneumonia case definitions.[80]

Use of supplemental oxygen is life-saving, but is not universally available in LMICs; it is estimated that use of supplemental oxygen systems could reduce mortality in children with hypoxic pneumonia by 20%.[81] Identifying systems capacity to increase availability of oxygen in health facilities, and

identifying barriers to further implementation are among the top 15 priorities for future childhood pneumonia research.[82] However, as up to 81% of pneumonia deaths in 2010 occurred outside health facilities,[5] there are major challenges with access to health services, and health-seeking behavior of vulnerable populations. Identifying and changing the barriers to accessing health care is an important area with potential impact on the survival and health of the most vulnerable children.[82]

2.10 Conclusion

Much progress has been made in decreasing deaths due to childhood pneumonia. Improved socioeconomic status and vaccinations, primarily the conjugate vaccines HiBCV and PCV, have led to substantial reductions in the incidence and severity of childhood pneumonia. Stronger strategies to prevent and manage HIV have reduced HIV-associated pneumonia deaths. Childhood pneumonia due to pneumococcus and Hib have decreased following rollout of PCV and HibCV. However, despite the substantial changes in incidence, etiology and radiology globally, there remain inequities in access to care and availability of effective interventions especially in LMICs. Effective interventions need to be more widely available, and new interventions developed for the residual burden of childhood pneumonia.

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Contributors

DLR performed the literature review and drafted the manuscript. HJZ directed and developed the concepts through discussion and subsequent drafts.

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Declaration of interests

The authors declare that they have no conflicts of interest

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Chapter 3

Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study

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3.1 Abstract

Background

Childhood pneumonia produces substantial mortality and morbidity. Accurate measurements of pneumonia incidence are lacking in low- and middle-income countries (LMIC), particularly after pneumococcal conjugate vaccine (PCV) implementation. This study aimed to describe incidence, severity and risk factors for pneumonia in the first year of life in children enrolled in a South African birth cohort.

Methods

Pregnant women living in a peri-urban area of South Africa were enrolled in a birth cohort, the Drakenstein Child Health Study. Mother-infant pairs were followed till 1 year of age; data on risk factors and respiratory symptoms were collected. Children received 13-valent PCV according to national immunisation schedule. Pneumonia surveillance systems were established. Ambulatory and hospitalized pneumonia episodes were documented. Pneumonia incidence rate ratios were calculated using mixed-effect Poisson regression.

Results

From May 2012 till May 2014, 697 children accrued 513 child-years of follow-up. Maternal smoking (24%) and HIV infection (19%) were common; no infant was HIV-infected. There were 141 pneumonia episodes, incidence 0.27 e/cy, (95% CI 0.23 –0.32); 32 cases were severe pneumonia, incidence 0.06 e/cy, (95% CI 0.04 – 0.08). There were 2 pneumonia deaths (1.4%). Maternal HIV, maternal smoking, male sex and malnutrition were associated with an increased incidence of pneumonia.

Conclusion

Pneumonia incidence was high in the first year of life, despite a strong immunisation program including PCV13. Risk factors for pneumonia amenable to interventions were identified.

3.2 Introduction

Childhood pneumonia is the leading cause of mortality in children accounting for approximately 17% of 6.3 million child deaths in 2010, more than HIV, measles and malaria combined.[1,2] Pneumonia also contributes substantially to health care utilisation in childhood, with an estimated 120 million episodes annually.[3] There is a disproportionately high burden among African children, with 36 million pneumonia cases and 600 000 pneumonia-associated deaths annually.[3] Chronic respiratory complications such as bronchiectasis occur commonly following childhood pneumonia, in up to 13% of hospitalized children.[4] Understanding the incidence and severity of pneumonia is therefore important to identify preventive interventions, for health systems planning and for burden of disease projections.

Longitudinal community-based studies with reliable measurements of pneumonia incidence are rare in low and middle income countries (LMIC).[5] Estimates of pneumonia incidence have therefore been modelled, based on previous incidence rates and risk factor prevalence. The most recent global estimate of pneumonia incidence in children under-5 years of age from LMIC was 0.22 episodes per child year (e/cy), with 11.5% meeting criteria for severe disease. The country-specific estimate for South Africa was 0.14 e/cy, with 11.1% of cases defined as severe.[6]

Randomised controlled trials of pneumococcal conjugate vaccination (PCV), using 7-valent (PCV7) or 9-valent (PCV9) vaccine, reported marked decreases in the incidence of clinical or radiologically-confirmed pneumonia, and in pneumonia hospitalizations.[7-11] Following introduction of PCV7, then PCV10 and PCV13, into national immunization programmes, substantial reductions in the incidence and severity of childhood pneumonia have been reported in high income countries,[12-15] as well as in Uruguay[16] and Brazil.[17] However there are limited data from sub-Saharan Africa, despite the continent's substantial burden of childhood pneumonia, and high incidence of severe disease.

The South African expanded program on immunisation (EPI) prescribes 4 doses of 5-vaccine combination (diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b and inactivated polio vaccine) given at 6, 10, 14 weeks and 18 months, and measles vaccine at 9 and 18 months. PCV7 was introduced in April 2009 with a novel schedule (6 weeks, 14 weeks, 9 months, with no catch-up doses given); this was replaced by PCV13 in June 2011.[18] A single-dose PCV13 catch-up vaccination was conducted for children aged 18 to 35 months from February to May 2012.

The Drakenstein Child Health Study (DCHS) is a unique South African birth cohort study which aims to investigate the incidence and long-term consequences of childhood pneumonia. We set out to examine the incidence and severity of early life pneumonia in this setting, as well as to examine

associations involving established sociodemographic, clinical, and behavioural risk factors for childhood pneumonia.

3.3 Methods

The DCHS is a birth cohort situated in Paarl, a peri-urban area 60km outside Cape Town, South Africa.[19] Study sites are located in two clinics, TC Newman and Mbekweni, approximately 5 kilometres apart and serving two separate communities with combined population of about 200 000. The residents of both areas have low socio-economic status, but are ethnically, linguistically and culturally heterogeneous. The first clinic serves a population which is mostly Afrikaans-speaking, mixed-race individuals; the second clinic's population is predominantly isiXhosa-speaking black Africans.[18]

From March 2012, pregnant women between 20 and 28 weeks gestation and attending antenatal care at one of the two clinics were enrolled, and followed through pregnancy and childbirth. Exclusion criteria were age less than 18 years and intention to leave the area within 1 year. Questionnaires on maternal health were administered and antenatal data collected.

Obstetric care was provided at a single regional hospital, Paarl Hospital where all births occurred; detailed birth information was obtained at the time of delivery. Infant follow-up visits occurred at 6, 10 and 14 weeks; and at 6, 9 and 12 months of age. [18] Interviews were conducted by trained study nurses in the mother's home language. Data on environmental exposures, pneumonia risk factors, anthropometry and the child's respiratory symptoms were collected at scheduled visits. Missed visits were re-booked using a study cellular phone network system or using study community-based field workers.

Mothers were counselled regarding respiratory symptoms at every visit, and advised to attend the study site or contact the study staff whenever the child developed cough or difficulty breathing, in addition to scheduled study visits. Study nurses were trained to diagnose pneumonia or severe pneumonia according to World Health Organisation (WHO) clinical case definitions.[20] Pneumonia was diagnosed in children with cough or difficulty breathing and age-specific tachypnoea ($\geq$ 50 breaths per minute for children 2-12 months) or if the child had lower chest indrawing. Severe pneumonia was diagnosed in children under 2 months with tachypnoea ($\geq$60 breaths per minute) or lower chest wall indrawing, or in children of any age if the child had a general danger sign (cyanosed, unable to drink, seizures or decreased level of consciousness).[20] The decision to hospitalize a child was made by the treating doctor; indications included severe pneumonia, hypoxia

(oxygen saturation of less than 92% in room air), or poor social circumstances in which ambulatory treatment was not feasible. Events that occurred more than 14 days after hospitalization or a prior event were considered to be new-onset, community acquired pneumonia.

An active surveillance system was established to detect participants with pneumonia or severe pneumonia. Study staff undertook pneumonia surveillance at primary care clinics and at Paarl Hospital on weekdays during working hours; surveillance continued at Paarl Hospital after hours and over weekends when clinics were closed. If a participant attended a primary health care clinic or the emergency unit at Paarl Hospital, the health care provider could contact the study nurse on the 24-hour cellular phone number. Mothers were given the cellular phone number to enable them to contact the study nurse on call if their child became ill. The study doctor provided regular training for all primary health care nurses on the accurate assessment of symptoms and signs in young children, and to ensure birth cohort participants were referred to the research study site when pneumonia or severe pneumonia was diagnosed.

Ethical considerations

Ethical approval was obtained from University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC REF 401/2009 and REF 651/2013) and the Provincial Child Health Research committee. Mothers gave written informed consent at enrolment.

Statistical analysis

The overall sample size for the DCHS is 1000 mother-infant pairs to provide at least 550 pneumonia episodes; this preliminary analysis was completed after 500 child-years of follow-up had been accrued in order to assess pneumonia incidence with precision of ±0.05 cases/child-year. Based on vaccine studies, the incidence of clinically defined pneumonia or severe pneumonia was expected to be approximately 10% lower in this vaccinated cohort than published pneumonia incidence estimates prior to PCV introduction. Significant associations of pneumonia with maternal smoking status, household crowding, low birth weight and suboptimal breastfeeding were expected.

For exploratory data analysis, continuous variables were summarized as medians with interquartile ranges (IQR), and categorical variables as percentages with 95% confidence intervals (CI). Medians were compared with rank sum tests and proportions with chi-square tests. Z-scores were derived from the WHO child growth standards[21] at birth and at every follow up visit; the median of all the weight-for-age Z scores for each child was used to summarize nutrition status over the duration of follow-up. Children were considered underweight or stunted if weight-for-age and length-for-age Z scores were less than -2. Follow-up was censored at last visit seen, death or 1 year of age. In analysis,

observation on each child was divided into one-month intervals, with 6299 intervals clustered around 697 infants. Factors associated with pneumonia events were analysed for the whole cohort and by study site. Multivariable modelling of pneumonia incidence used mixed-effect Poisson models, including a random intercept for each infant; results are presented as incidence rate ratios with 95% CI. Because weight-for-age Z scores are likely to be a causal intermediate through which different risk factors influence pneumonia risk, separate models were developed to include weight-for-age Z score. Seasonal incidence comparisons analysed December through February as summer, March through May as autumn, June through August as winter and September through November as spring. All analyses were done in Stata 11 (College Station, TX).

Role of the funding source

The study sponsors had no role in the study design; the collection, analysis, and interpretation of the data; in the writing of the report; or in the decision to submit for publication. Authors had access to all the data in the study and shared final responsibility for the decision to submit.

3.4 Results

Between May 2012 and May 2014, 697 infants accrued 513 child-years of follow up. There were baseline differences between the two enrolment sites in mothers and infants, table 3.1. Exposure to environmental tobacco smoke was common; 166 mothers (24%) self-reported smoking, with higher rates at TC Newman, while 63% of children were reported to share a household with at least one cigarette smoker. Median birth weight and infant nutritional status were lower at TC Newman compared to Mbekweni, table 3.1. One hundred and thirty mothers (19%) were HIV-infected, with higher prevalence at Mbekweni, table 3.1. No infants were HIV-infected. While 616 mothers (88%) initiated breastfeeding, only 163 of 519 (31%) were exclusively breastfeeding by 4 months, and 48 of 447 (11%) by six months.

In the first year of life, 13 infants died, and 89 were disenrolled: 12 mothers withdrew consent, 51 relocated, 17 were unable to be contacted, 9 for other reasons, supplementary figure 1. Most children who were disenrolled remained in follow-up and in contact with the study staff until the date of termination, so their health outcomes are known.

Immunisation coverage of primary series vaccinations was high (98% at 6 weeks, 94% at 10 weeks and 89% at 14 weeks). However vaccines were delayed by more than 2 weeks in 7% (6 weeks), 15% (10 weeks) and 21% (14 weeks). Coverage of 9 month vaccination was lower: 78% of children received a 9 month vaccine; 10% of 9 month vaccines were given late, figure 1.

One hundred and sixty-five illness episodes met the clinical case definition of pneumonia. Twenty-four events occurred on the first day of life. In 18 cases, tachypnoea and respiratory distress were due to pre-term delivery, and were treated with nasal continuous positive airway pressure (CPAP); 9 infants also required surfactant therapy. Other causes of respiratory distress on the first day of life included congenital pneumonia in two babies, and one congenital diaphragmatic hernia.

Excluding 24 events that occurred on the first day of life, there were 141 cases of community acquired pneumonia (CAP) during the first year, an incidence of 0.27 e/cy (95% CI 0.23 – 0.32). There were 7 cases of CAP in the first month of life, an incidence of 0.12 e/cy, table 3.2. The incidence of CAP from the second month till 1 year of age was 0.29 e/cy (95% CI 0.25 – 0.35). Incidence was lowest in the first month, highest in the third month and decreased to 0.24 e/cy in the 12th month, figure 2. The 141 CAP episodes occurred in 109 children; 22 children had 2 episodes, 9 children had 3, and 1 child had 4 pneumonia events. In 4 events, tachypnoea improved after bronchodilator administration. Pneumonia incidence in winter was nearly 5-times that in summer, table 3.2.

Thirty-two (23%) CAP events met WHO criteria for severe pneumonia; the incidence of severe pneumonia was 0.06 e/cy (95% CI 0.04 – 0.08). Twenty-six severe episodes (81%) occurred in the first 2 months of life; 21/26 (81%) of infants under 2 months had lower chest wall indrawing. In this cohort of young infants, WHO severe pneumonia did not correlate well with hypoxia: 10 of 32 infants (31%) who met the criteria for severe pneumonia had oxygen saturations of less than 92%, with similar proportion in those under 2 months (8/26, 31%), vs over 2 months, (2/6, 33%). In addition, only 13 of 23 (57%) of children with documented hypoxia met criteria for severe pneumonia.

Eighty-six pneumonia events (61%) were managed as outpatients and 55 (39%) required hospitalization. Children hospitalized with pneumonia were younger than those with ambulatory pneumonia, had higher median respiratory rates, lower median oxygen saturations, and lower weight-for-age and height-for-age Z scores, table 3.3. Wheeze was present in 92/141 (65%) of pneumonia cases. Wheeze was less common at the time of severe pneumonia events (14/32, 44%) than at pneumonia events (78/109, 72%, p=0.004). Wheeze was present in 82/115 (71%) infants older than 2 months, compared to 10/26 (37%) of those under 2 months, p=0.001.

The median length of hospitalization was 3 days (IQR 2 – 5 days). There were 2 pneumonia-related deaths, giving a case fatality ratio of 1.4% of all CAP or 6% of severe cases. The first was a 3 week-old child with pneumococcal septicaemia and empyema; the second was a 6 week-old child with a congenital cardiac lesion, who died *en route* to hospital. Both children died before their first PCV vaccination; post mortem examinations could not be obtained.

Pre-term delivery, underweight and stunting were associated with increased incidence of pneumonia; higher maternal educational achievement was associated with decreased incidence of pneumonia, table 3.2. There were few pneumonia events in children with missed or delayed vaccinations (1 pneumonia event in a child with delayed 6-week PCV dose, 7 events in children with delayed 14-week PCV dose, table 3.2). Children older than 14 weeks with delayed second dose of PCV had increased incidence of pneumonia compared to those who received vaccinations on time, but this was not statistically significant, table 3.2.

In multivariable analysis, age, male sex, maternal HIV status and self-reported smoking were the strongest risk factors for pneumonia, table 3.4. Breastfeeding duration was not significant in the adjusted model, but was included as a known pneumonia risk factor. When weight-for-age Z score was included in the model as a potential causal intermediate, it appeared strongly associated with pneumonia incidence, and associations involving other risk factors were attenuated. HIV exposure and young age were the strongest risk factors for severe pneumonia, table 3.4.

3.5 Discussion

This birth cohort study provides one of the first measurements of the incidence of pneumonia in infants following PCV13 introduction in a LMIC setting. There was a high incidence of pneumonia during the first year of life, and a high proportion were severe pneumonia or required hospitalization. This occurred despite high immunisation coverage and a strong primary health care program with effective prevention of vertical transmission of HIV. The pneumonia incidence of 0.27 e/cy is nearly double the estimated incidence for under-5 year old South African children (0.14e/cy), and higher than the developing world median estimate of 0.22 e/cy,[6] which were calculated before PCV implementation. This may partly reflect that our incidence was calculated for the first year of life, during which childhood pneumonia incidence is highest.[22] Moreover, the incidence of pneumonia was highest under 6 months of age, reflecting the increased vulnerability of young children to pneumonia and severe pneumonia. The incidence was also substantially higher than that described in the first year of life in high income countries (HIC), which ranged from 0.006 to 0.085 e/cy.[23] However the incidence is comparable to that described in some other LMICs in the first year of life, which may reflect differences in populations, diagnostic certainty or risk factors for pneumonia.[24-26]

The high incidence of pneumonia occurred despite high immunisation coverage, including PCV13, acellular pertussis, *Haemophilus influenzae* type b conjugate and measles vaccines. Delayed vaccination may increase vulnerability to pneumonia due to lack of protective immunity.[27,28] This study was not designed to assess the effectiveness of increasing number of PCV doses; vaccine

coverage was high, and few pneumonia events occurred among children with missed or delayed vaccinations. For optimal protection against pneumonia, completion of a primary 2 +1 series of PCV is required.[29,30] In support of this, the incidence of pneumonia was lower in children who had received 2 or 3 PCV immunisations compared to those who had received a single dose. However, young age may be a confounding variable as children with fewer immunisation doses were younger than those who had completed a primary series.

Despite the young age of the cohort, case fatality ratios for overall pneumonia cases and for severe pneumonia cases were lower than the global average for children under 5 years with severe pneumonia.[3] This probably reflects high immunisation coverage (reducing the severity of pneumonia); good access to health care by birth cohort participants; and a strong primary health care program, ensuring timely availability of antibiotic therapy and oxygen at community clinics and referral to hospital when indicated.

Known risk factors for pneumonia were confirmed in this cohort, and the magnitude of their effects quantified in the context of a strong primary health care program. No child was HIV-infected, despite a high prevalence of HIV infection in pregnant women; this reflects a strong prevention of mother-to-child-transmission program. However, HIV-exposure *per se* was a significant independent risk factor for pneumonia, especially for severe pneumonia, even after adjusting for feeding choice. This may be due to developmental abnormalities of the innate[31] or adaptive[32] immune systems, lack of protection from maternal antibodies or increased exposure to infectious diseases through living in a household with a member who is HIV-infected. This finding highlights a group of children who although they are not HIV-infected, may be especially vulnerable to developing severe disease. Males had higher incidence of pneumonia than females; this may be due to differences in intrinsic immune or inflammatory responses,[33,34] or possible differences in lung structure or function.[35] Maternal smoking was associated with increased pneumonia incidence; possible mechanisms include *in utero* effects of maternal smoking which reduces infant lung growth,[36] or post-natal exposure to tobacco smoke predisposing to respiratory infection or development of wheezing illness.[37] Higher maternal education was significantly associated with decreased incidence of pneumonia, suggesting that maternal education may have a direct effect on child health.

Exclusive breastfeeding (EBF) for 6 months is recommended for the reduction of pneumonia incidence and mortality in LMICs.[38] As previously described for this district,[39] a low proportion of participants sustained EBF for 6 months. The incidence rate ratio from Poisson models regression suggests sub-optimal breastfeeding is associated with 70% increased incidence of pneumonia, but this did not reach statistical significance.

Pre-term delivery and low birth weight are recognised risk factors for pneumonia.[40] In addition, underweight and stunting, markers of both low birth weight and post-natal growth and nutrition, were strongly associated with increased pneumonia incidence. This reflects the well-described association of malnutrition with pneumonia incidence and severity,[41] possibly due to impaired immunity or micronutrient deficiency. Further study of the nutritional factors associated with pneumonia risk in this cohort is underway.

Wheezing occurred commonly in children with pneumonia. This is not unexpected, as prior studies of children with pneumonia, including an analysis of more than 4000 episodes of hospitalization for lower respiratory tract infection in young South African children enrolled in a vaccine study, reported concomitant wheezing in approximately 50% of children who met the WHO clinical case definition of pneumonia.[42-45] The high incidence of wheezing may reflect viral infection (alone or with other pathogens) as a cause of pneumonia; or that the relatively small airways of young children may become obstructed due to infection or resulting inflammation. Further study of the aetiology of pneumonia episodes in our study is underway. As this study aims to report all-cause pneumonia, children with wheezing who met the WHO clinical case definition for pneumonia were included. Moreover, the current evidence indicates that viral illness, such as that produced by RSV, constitutes a very large global burden with a substantial case fatality rate especially in LMICs.[46] While distinguishing bronchiolitis from pneumonia is not possible using the WHO case definitions, this represents a spectrum of lower respiratory tract illness with substantial morbidity and mortality.

Limitations of this study include the possibility of misclassification of pneumonia cases due to differing clinical case definitions.[6] To limit misclassification, standard recently revised WHO clinical case definitions were used to enable standardised diagnosis and comparison with other data and pneumonia incidence research. These case definitions were designed for maximum sensitivity for pneumonia diagnosis, but have lower specificity than other measures such as radiological pneumonia. A strength of this study is the consistent use of such case definitions by study staff. While use of these standardised definitions may lead to overdiagnosis of pneumonia, these are widely used globally for diagnosis and management, and enable comparison with data from other regions.

Study staff were trained and assessed in application of these case definitions and strong pneumonia surveillance systems were established. Although study nurses monitored every illness episode in birth cohort participants, some pneumonia events may have been missed. The 17 participants who were lost to follow up may have had pneumonia events that were not reported to the study team; however, as these comprised only 2.4% of the cohort, these are unlikely to have substantially affected the results. It is unlikely that hospitalized events would have been missed as Paarl Hospital is the only public hospital in the area; however some ambulatory events may have been under-counted if mothers

did not seek care. The incidence of 0.27 e/cy may therefore represent the minimum incidence of pneumonia in this cohort.

The generalizability of these results to other areas in Africa may be limited. However, a strength of this study is that it was conducted across 2 heterogenous communities with meticulous measurement of a wide range of risk factors. This allows wider generalizability to areas with similar risk factor distributions. In addition, sub-group incidence estimates can be used to guide disease burden modelling in areas with different prevalences of risk factors.

This is the first birth cohort study in a LMIC with a well-established primary health care system and an immunisation program including new conjugate vaccines. In the first year of follow-up, pneumonia incidence was high despite good vaccination coverage, and was strongly associated with risk factors amenable to intervention. Prevention of childhood pneumonia through public health interventions addressing maternal smoking cessation, prevention of HIV transmission, promotion of breastfeeding, child nutrition and timely vaccination should be strengthened. To complement these findings, incidence estimations after the age of 1 year, and investigation of the infectious aetiology of childhood pneumonia in the context of high conjugate vaccination coverage should be prioritised for further research.

3.6 Contributors and acknowledgements

Contributors

DLR was the study clinician and coordinator; conducted preliminary data analysis under the supervision of LM; and was primarily responsible for interpretation of results and drafting of the manuscript. HJZ is the principal investigator of the DCHS; she conceived and designed the study and obtained funding together with MPN, who is the lead microbiologist and LM who leads the epidemiological and analyses aspects. HJZ, MPN and LM provided operational oversight. All authors reviewed, contributed to and approved the final manuscript.

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Declaration of interest

The authors have no conflicts of interest to declare.

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3.7 Research in context

Literature review

We searched Pubmed for articles published in English up till August 2013 using the search terms "child" AND "pneumonia". We identified some high quality systematic reviews on the incidence and global burden of childhood pneumonia. However, the published evidence predominantly relied on modelled estimates of pneumonia incidence or extrapolation from child mortality statistics. There is a lack of accurate longitudinal data on the incidence of pneumonia in children and on severity of disease especially following introduction of childhood pneumococcal conjugate vaccine in low and middle income countries (LMICs).

Interpretation

This is one of the first birth cohort studies to longitudinally investigate the incidence, severity and risk factors for childhood pneumonia in a LMIC after introduction of new conjugate vaccines. Using standard World Health Organisation clinical case definitions, a high incidence of pneumonia was observed, with a high proportion of severe pneumonia cases in the first year of life. Exposure to environmental tobacco smoke, young age, male gender and maternal HIV infection were associated with pneumonia or severe pneumonia. Childhood pneumonia remains an important public health problem despite the introduction of new conjugate vaccines. Attention to the broader determinants of childhood pneumonia is needed to prevent this disease burden.

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3.9 Tables and figures

Table 3.1: Characteristics of mothers and infants by study site

Maternal characteristics	Clinic 1 (TC Newman) n=359	Clinic 2 (Mbekweni) n=338
Race / ethnicity: Black African, n(%) **Mixed race, n(%)**	5 (1.4) 353 (99)	337 (99) 1 (0.3)
Formal employment, n(%)	109 (30)	69 (20)
Receives national child support grant, n(%)	200 (56)	188 (56)
Formal housing, n(%)	266 (74)	182 (54)
Household crowding: **3 or fewer people, n(%)** **4 or 5 people, n(%)** **More than 5 people, n(%)**	 79 (22) 138 (39) 141 (39)	 145 (43) 106 (31) 86 (26)
Maternal education: **Primary school only, n(%)** **Some secondary school, n(%)** **Finished secondary school, n(%)**	 25 (7) 179 (50) 155 (43)	 35 (10) 182 (54) 120 (36)
SES quartile: Lowest SES, n(%) **Moderate low SES, n(%)** **Moderate high SES, n(%)** **Highest SES, n(%)**	52 (14) 96 (27) 88 (25) 123 (34)	107 (32) 106 (31) 73 (22) 51 (15)
HIV infected, n(%)	9 (2.5)	121 (36)
Maternal self-reported smoker, n(%)	162 (45)	14 (4)
Infant characteristics		
Male, n(%)	206 (57)	166 (49)
Pre term (<37 weeks), n(%)	52 (15)	44 (13)
Low birth weight (<2500g), n(%)	70 (20)	38 (11)
Birth weight: median (IQR)	2.99kg (2.59 – 3.40)	3.12kg (2.77 – 3.45)
Weight for age Z score: Median (IQR)	-0.45 (-1.33 to 0.25)	-0.30 (-1.0 to 0.43)
Height for age Z score: Median (IQR)	-0.68 (-1.67 to 0.1)	-0.18 (-1.26 to 0.59)
Feeding choice: Never breast fed, n(%) **Completed 6 month feeding questionnaire, n=447:** **Exclusive breast for 6 months, n (%)** **Mixed feeding at 6 months, n (%)** **Exclusive formula feeding at 6 months, n(%)**	31 (9) (n=231) 21 (9) 139 (60) 71 (31)	105 (31) (n=216) 27 (13) 66 (31) 123 (57)
Age (days) at censoring: Median (IQR)	358 (186 – 365)	308 (166 – 365)
Vaccination coverage: **All primary series doses given on time, n(%)** **All primary series doses given, some doses late, n(%)** **At least 1 primary series dose missed, n(%)**	(n=329) 196 (60) 154 (16) 79 (24)	(n=308) 206 (67) 73 (24) 29 (9)

SES = socio-economic status
IQR= Interquartile range

Table 3.2: Incidence of pneumonia in the cohort by maternal and infant characteristics

	Pneumonia events (n=141)	Person time (years)	Incidence pneumonia e/cy[1]	Incidence rate ratio (95% CI)
Study site: Mbekweni	55	245.0	0.22 (0.17 – 0.29)	1
TC Newman	86	267.8	0.32 (0.26 – 0.40)	1.43 (1.01 – 2.04)
Season: Summer	14	130.7	0.11 (0.06 – 0.18)	1
Autumn	39	148.7	0.26 (0.19 – 0.36)	2.45 (1.30 – 4.88)
Winter	54	102.5	0.53 (0.40 – 0.69)	4.92 (2.69 – 9.59)
Spring	41	118.1	0.35 (0.25 – 0.47)	3.24 (1.73 – 6.44)
Mother non-smoker	87	378.1	0.23 (0.18 – 0.28)	1
Mother self-reported smoker	54	133.0	0.41 (0.30 – 0.53)	1.76 (1.23 – 2.50)
Maternal education				
Primary school only	27	45.2	0.60 (0.39 – 0.87)	1
Some secondary	74	266.7	0.27 (0.22 – 0.35)	0.46 (0.30 – 0.75)
Completed secondary	40	199.9	0.20 (0.14 – 0.27)	0.33 (0.20 – 0.57)
Sex: Female	44	245.4	0.18 (0.13 – 0.24)	1
Male	97	267.4	0.36 (0.29 – 0.44)	2.02 (1.40 – 2.96)
Child HIV-unexposed	106	413.8	0.26 (0.21 – 0.31)	1
Child HIV exposed[2]	35	99.0	0.35 (0.25 – 0.49)	1.38 (0.91 – 2.03)
Child age: Under 1 month	7	58.2	0.12 (0.05 – 0.25)	1
1 – 6 months	106	292.9	0.36 (0.30 – 0.44)	3.00 (1.41 – 7.67)
6 – 12 months	28	161.7	0.17 (0.12 - 0.26)	1.44 (0.61 – 3.90)
Full term	96	392.53	0.24 (0.20 – 0.30)	1
Pre term (<37 weeks)	54	120.28	0.37 (0.27 – 0.500	1.52 (1.04 – 2.20)
Birth weight > =2500g	110	430.18	0.26 (0.21 – 0.31)	1
Low birth weight (<2500g)	31	82.62	0.38 (0.25 – 0.54)	1.47 (0.95 – 2.20)
Anthropometry:				
Weight-for-age				
Z score greater than -2	115	466.1	0.25 (0.20 – 0.30)	1
Z score less than -2	26	46.7	0.55 (0.36 – 0.82)	2.25 (1.41 – 3.48)
Length-for-age				
Z score greater than -2	104	426.5	0.24 (0.20 – 0.30)	1
Z score less than -2	37	86.3	0.43 (0.30 – 0.59)	1.76 (1.17 – 2.58)
Feeding:				
Exclusive breast for 6 months	8	44.57	0.18 (0.07 – 0.35)	1
Any formula milk before 6 months	133	468.0	0.28 (0.24 – 0.34)	1.58 (0.78 – 3.75)
PCV vaccine doses:				
Age 6-14 weeks:				
First dose PCV not given	1	2.04	0.50 (0.01 – 2.77)	1
First dose PCV given on time	44	86.72	0.51 (0.37 – 0.68)	1.04 (0.18 – 41.8)
Age >14 weeks				
2nd dose PCV not given	7	19.82	0.35 (0.14 – 0.73)	1
2nd / 3rd doses PCV on time	61	276.49	0.22 (0.17 – 0.28)	0.62 (0.29 – 1.62)

1: E/cy = episodes per child-year
2: All HIV-exposed children were HIV-uninfected
PCV - Pneumococcal conjugate vaccine

Table 3.3: Risk factors for and clinical features of ambulatory and hospitalized pneumonia cases in the cohort

Risk factors	Ambulatory pneumonia cases n= 86	Hospitalized pneumonia cases n=55	p-value
Age (months), median (IQR)	4.52 (2.79 – 5.87)	2.49 (1.57 – 6.62)	0.01
HIV exposed, n (%)	19 (22)	16 (29)	0.35
Pre-term (<37 weeks), n (%)	12 (14)	15 (27)	0.05
Low birth weight (<2500g), n (%)	16 (19)	15 (27)	0.23
Maternal self-reported smoking, n(%)	32 (37)	22 (40	0.74
4 or more people in the house, n (%)	62 (72)	46 (83)	0.11
SES quartiles Lowest, n (%) **Moderate low, n (%)** **Moderate high, n (%)** **Highest, n (%)**	23 (27) 30 (35) 19 (22) 14 (16)	19 (35) 13 (24) 15 (27) 8 (15)	0.47
Feeding choice: **Exclusive breast for 6 months, n (%)** **Mixed feeding, n (%)** **Never breastfed, n (%)**	 3 (3) 64 (74) 19 (22)	 5 (9) 36 (65) 14 (25)	0.30
Clinical features			
WHO severe pneumonia, n (%)	12 (14)	20 (36)	0.002
Weight-for-age Z score, median (IQR)	-0.2 (-1.2 to 0.55)	-1.1 (-1.81 to 0.14	0.003
Height-for-age Z score, median (IQR)	-0.69 (-2.1 to 0.54)	-2.2 (-4.1 to 0.02)	0.002
Respiratory rate, median (IQR)	56 (52 – 62)	62 (56 – 68)	0.002
Lower chest wall indrawing, n (%)	36 (42)	45 (81)	<0.0001
Wheeze, n (%)	58 (67)	34 (62)	0.49
Fever>38°, n (%)	17 (24)	26 (49)	0.004
Unable to feed, n (%)	7 (8)	12 (22)	0.03
Oxygen saturation (lowest), median (IQR)	97 (94 – 98)	94 (90 – 96)	0.001

Table 3.4: Incidence rate ratios (IRR) with 95% confidence intervals (CI) for severe pneumonia, pneumonia and total pneumonia events.

All models are adjusted for site of enrollment. Model A includes risk factors shown, and Model B includes risk factors shown as well as weight for age Z score as an intermediate variable through which risk factors may influence pneumonia risk.

	Severe pneumonia	**Pneumonia**	**All pneumonia events: model A**	**All pneumonia events: mode B**
	IRR (95% CI)	IRR (95% CI)	IRR95% CI	IRR (95% CI)
Sex: Male	1.20 (0.55-2.62)	2.49 (1.52-4.08)	2.071.37-3.11	1.98 (1.32-2.99)
HIV-exposed	4.04 (1.51-10.80)	1.55 (0.81-2.96)	1.621.01-2.61	1.52 (0.98-2.36)
Maternal smoking	0.71 (0.28-1.79)	2.36 (1.45-3.82)	1.981.33-2.95	1.94 (1.32-2.83)
Any formula feeding before age 6 months	0.97 (0.23-4.12)	2.07 (0.70-6.17)	1.740.72-4.20	1.75 (0.73-4.14)
Child age (1-month units)	0.66 (0.54-0.80)	0.98 (0.92-1.03)	0.930.89-0.98	0.93 (0.88-0.98)
Weight for age Z score less than -2				1.79 (1.05-3.02)

Figure 3.1: Coverage of routine childhood vaccinations in the cohort through the first year of life (*Haemophilus influenzae* type b conjugate vaccine at 6. 10 and 14 weeks; pneumococcal conjugate vaccine at 6 weeks, 14 weeks and 9 months)

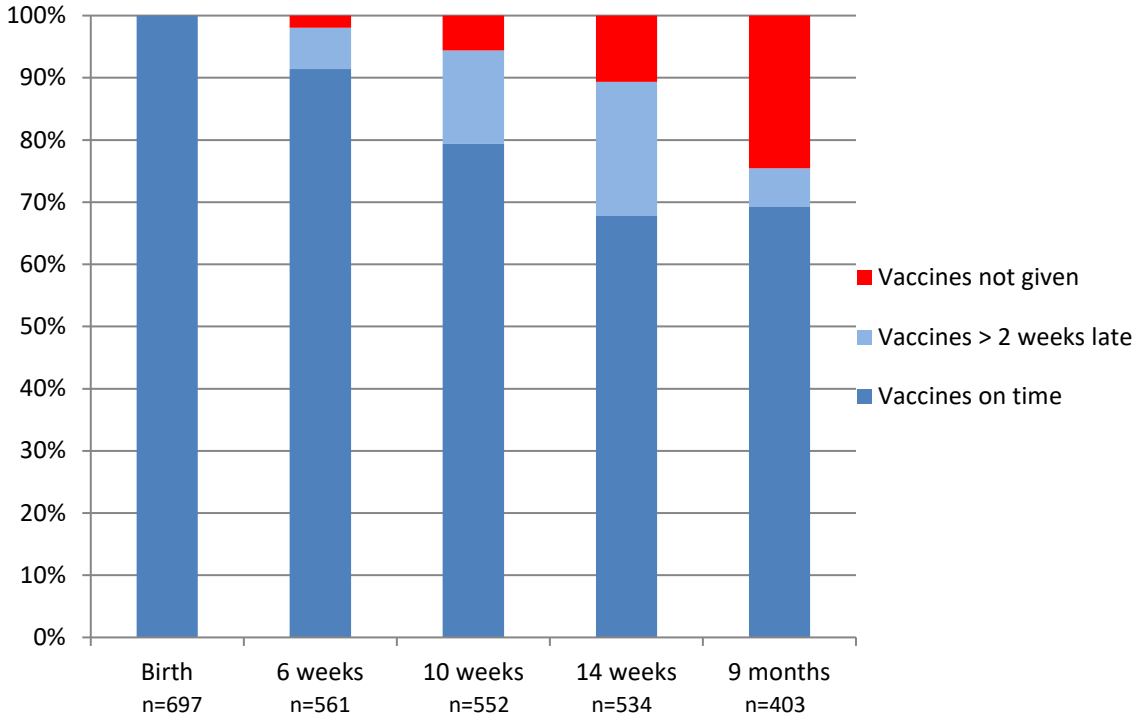
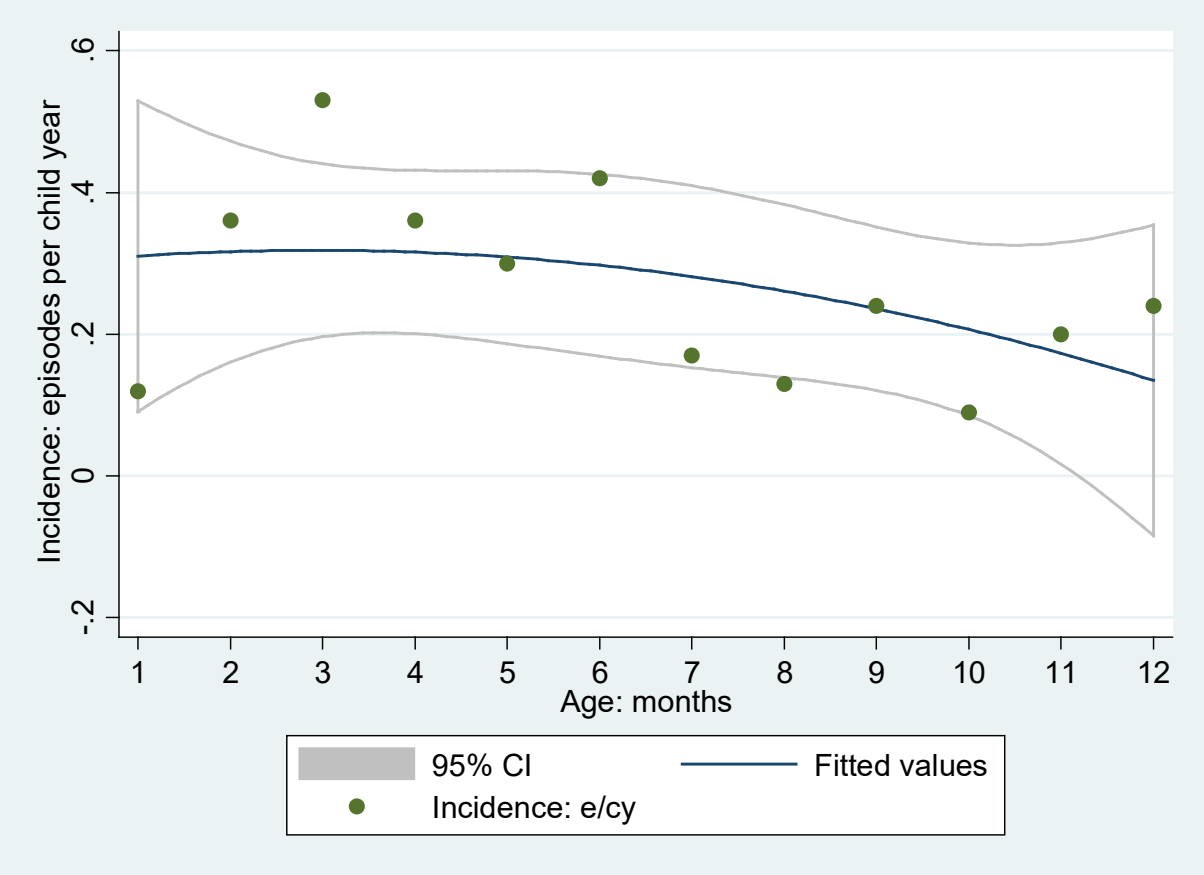
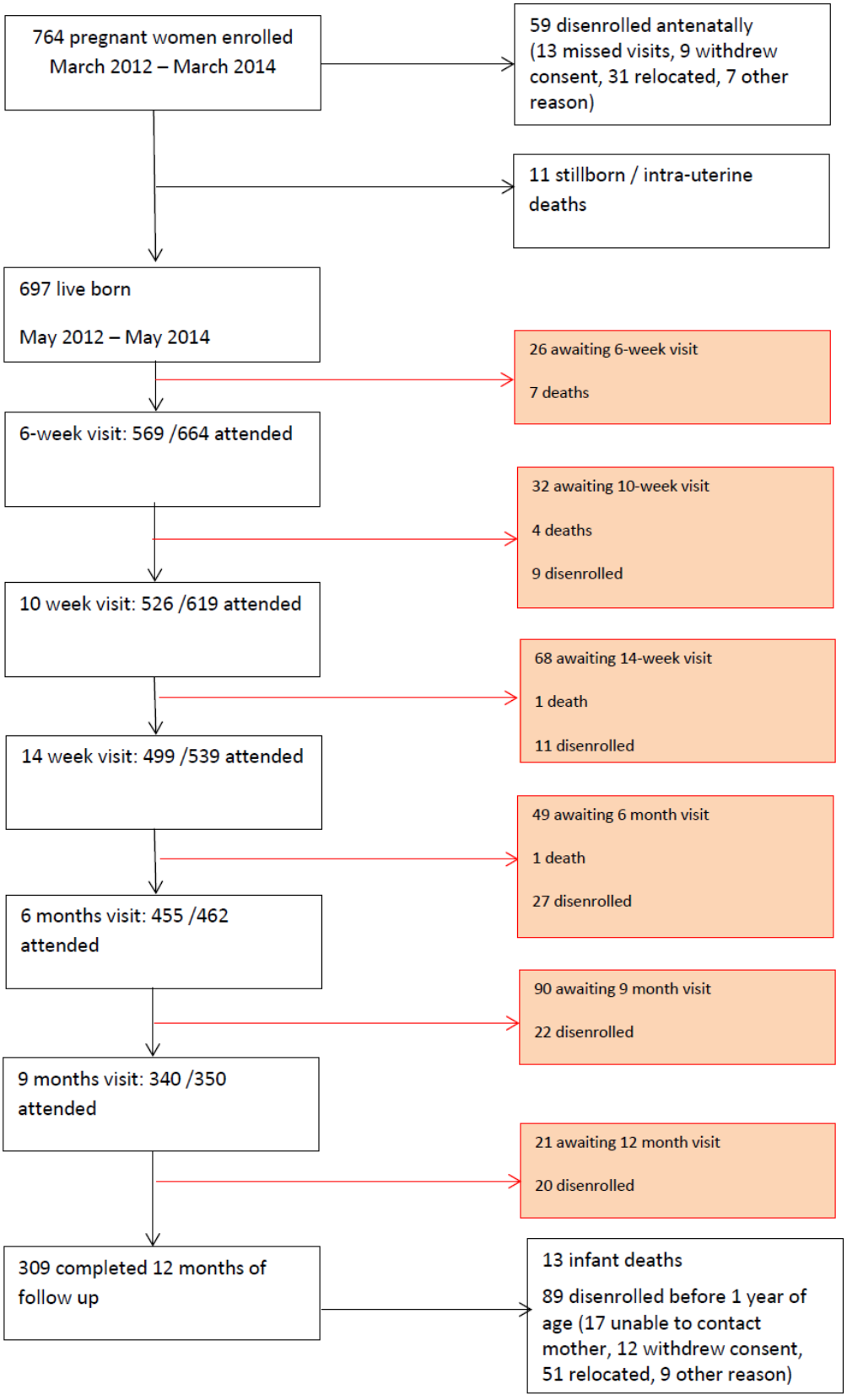


Figure 3.2: Incidence of pneumonia in the cohort during the first year of life



Supplementary figure 3.1: flow diagram of birth cohort retention (as of May 2014)



Supplementary table 3.1: STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies:* Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	48
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	48
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	49
Objectives	3	State specific objectives, including any prespecified hypotheses	49
Methods			
Study design	4	Present key elements of study design early in the paper	50
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	50
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	50
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	50-52
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	52
Bias	9	Describe any efforts to address potential sources of bias	52
Study size	10	Explain how the study size was arrived at	(This is a preliminary analysis –full cohort will be enrolled by February 2015)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	52

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	52
		(*b*) Describe any methods used to examine subgroups and interactions	52
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Suppl fig 3.1
		(b) Give reasons for non-participation at each stage	Suppl fig 3.1
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	52-53
		(b) Indicate number of participants with missing data for each variable of interest	Table 3.1
		(c) Summarise follow-up time (eg, average and total amount)	53
Outcome data	15*	Report numbers of outcome events or summary measures over time	53
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3.2
		(*b*) Report category boundaries when continuous variables were categorized	52
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	53-54
Discussion			
Key results	18	Summarise key results with reference to study objectives	54
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	54, 55
Generalisability	21	Discuss the generalisability (external validity) of the study results	57
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	58

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Chapter 4

Incidence of childhood pneumonia: facility-based surveillance estimate compared to measured incidence in a South African birth cohort study

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4.1 Abstract

Background

Pneumonia is the leading cause of childhood mortality and a major contributor to childhood morbidity, but accurate measurement of pneumonia incidence is challenging. We compared pneumonia incidence using a facility-based surveillance system to estimates from a cohort study conducted contemporaneously in the same community in Cape Town, South Africa.

Methods

A surveillance system was developed in 6 public sector primary care clinics and in a regional referral hospital to detect childhood pneumonia cases. Nurses recorded all children presenting to facilities who met World Health Organisation case definitions of pneumonia, and hospital records were reviewed. Estimates of pneumonia incidence and severity were compared with incidence rates based on active surveillance in the Drakenstein Child Health Study.

Results

From June 2012 until September 2013, the surveillance system detected 306 pneumonia episodes in children under 1 year, an incidence of 0.20 episodes per child year (e/cy) (95% CI 0.17 – 0.22 e/cy). The incidence in the cohort study from the same period was 0.27 e/cy (95% CI 0.23 – 0.32 e/cy). Pneumonia incidence in the surveillance system was almost 30% lower than in the birth cohort; incidence rate ratio 0.72 (95% CI 0.58 – 0.89). In the surveillance system 18% were severe pneumonia, compared to 23% in the birth cohort, rate ratio 0.81 (95% CI 0.55 –1.18).

Conclusion

In this setting facility-based pneumonia surveillance detected fewer cases of pneumonia, and fewer severe cases, compared to the corresponding cohort study. Facility pneumonia surveillance using data collected by local health care workers provides a useful estimate of the epidemiology of childhood pneumonia but may underestimate incidence and severity.

4.2 Introduction

Pneumonia is the largest single cause of child mortality outside of the neonatal period, accounting for 15% of the approximately 6.3 million global child deaths each year.[1,2] Pneumonia is also a major cause of childhood morbidity with approximately 120 million episodes of pneumonia occurring annually.[3] Up to 50% of consultations at health care facilities for sick children in low and middle income countries (LMICs) are due to acute respiratory infections.[4] Accurate measurement of the incidence of childhood pneumonia is important for allocation of resources, measurement of the impact of interventions such as new vaccines, identifying risk factors, and for health systems planning.

Estimating the incidence of pneumonia in LMICs can be challenging, with widely varying estimates.[5] Many studies report incidence of hospitalization[6] or of radiologically-confirmed[7] pneumonia, and do not quantify ambulatory events or events without radiological confirmation. Some studies have reported population-level incidence estimates using World Health Organisation (WHO) clinical case definitions in under-1 and under-5 year olds, but the incidence estimates are highly variable, reflecting large regional variations in pneumonia incidence[8]. Most population-level estimates of pneumonia incidence are extrapolated from national under-5 mortality estimates, prevalence of known pneumonia risk factors, and likely proportion of deaths due to pneumonia.[5] From the estimated number of pneumonia deaths, the number of severe pneumonia admissions and ambulatory pneumonia cases can be back-calculated.[9] A recent modelled estimate of pneumonia incidence for children younger than 5 years in South Africa was 0·14 episodes per child-year.[10] However reliance on modelled estimates of pneumonia incidence can be problematic as the pneumonia incidence models do not necessarily account for local high-prevalence risk factors (such as HIV infection) or changes to health care (such as introduction of 13-valent pneumococcal conjugate vaccine, PCV13).

Analysis of routinely-collected health systems data provides numbers of childhood pneumonia cases, and may be useful for defining the burden of disease in a district, but calculation of pneumonia incidence based on health service data is complicated by several challenges. These include well-documented concerns with the quality of routine health statistics in many settings, variations in health seeking behaviours, and difficulties in deriving accurate denominators for incidence estimation.[4] As a result of these concerns the most reliable method of determining childhood pneumonia incidence is through prospective studies with active pneumonia case finding, independent objective verification of clinical signs of pneumonia, and accurate measurement of the person-time at risk throughout follow up.[11]

The Drakenstein Child Health Study (DCHS), a birth cohort study to investigate the incidence, aetiology and long term consequences of childhood pneumonia, is being undertaken in South Africa.[12]

As part of this study, pneumonia cases were actively detected amongst children enrolled in the cohort. In parallel, a facility-based pneumonia surveillance system was established in the communities from which the birth cohort participants were recruited and followed. Here we describe the establishment and results of the pneumonia surveillance system, and compare the incidence of pneumonia detected through the surveillance system with that measured in the birth cohort in the first year of life.

4.3 Methods

The study was conducted in a peri-urban setting in the Western Cape province of South Africa, approximately 60 kilometres outside Cape Town. Two separate communities were included in both the birth cohort and surveillance system, including 6 primary care community clinics and the local secondary hospital which serves as a referral point for primary care services, including pneumonia. In one community, Mbekweni, health care was provided at 2 nurse-run primary health care (PHC) clinics. The other community, Paarl East, was served by a central nurse-run PHC clinic, and by 3 satellite PHC clinics. Nurses at these clinics treated paediatric presentations according to Integrated Management of Childhood Illness (IMCI) principles; children who met severity criteria were referred to Paarl Hospital. Clinics were open daily on weekdays; on weekends and afterhours, care was provided at Paarl hospital. The childhood immunization schedule included vaccinations against pertussis, *Haemophilus influenzae* type b, and measles, as well as PCV13 at 6, 14 weeks, and 9 months. There is very limited utilization of private sector health care services in these communities; individuals usually make use of a single designated clinic; antibiotics cannot be bought over the counter without a prescription.

Facility-based pneumonia surveillance system

A pneumonia surveillance system was established in the 6 clinics in the study area. Meetings and training sessions were held with the nursing staff at each clinic to train staff on WHO clinical case definitions.[13] Training sessions included video clips of children demonstrating clinical signs. Nurses at the 6 clinics were provided with simple data capture sheets to record information regarding each pneumonia episode that met the WHO criteria (cough or difficulty breathing with age-appropriate tachypnea or lower chest indrawing). Severe pneumonia classification was based on age and presence of clinical signs. For children aged less than 2 months, clinical signs included respiratory rate $\geq$60, severe chest indrawing, nasal flaring, grunting, or fever >37.5^{0}C. For children older than 2 months, clinical signs of severe pneumonia were lower chest wall indrawing, stridor in a calm child, or any general danger sign.[13] Children older than 2 months with lower chest wall indrawing but no other criteria for severity were retrospectively re-classified as "pneumonia" according to revised 2014 WHO case definitions.[13,14] The study doctor visited each clinic monthly, and provided on-site refresher training to the nurses. In addition, a local field worker visited each clinic weekly to collect

data capture sheets, reinforce the study aims, and encourage the nurses to continue with the surveillance. At Paarl hospital, data on pneumonia episodes was abstracted from hospital folders of children who met the case definitions and were resident in the catchment area. The child's folder number, date of birth and area of residence were recorded to prevent double-counting of pneumonia cases referred from a local clinic to the hospital. Facility-based pneumonia surveillance was conducted from June 2012 to Sept 2013 in the 6 community clinics and at Paarl Hospital.

Measurement of pneumonia incidence in the Drakenstein Child Health Study

The DCHS is a prospective birth cohort with the primary aim to investigate the incidence, aetiology and long-term consequences of childhood pneumonia. Pregnant women were enrolled during antenatal care and their children were enrolled from birth. Regular scheduled follow-up visits occurred through the first year of life at primary care clinics or at Paarl hospital.[12]

The method of pneumonia case detection in the surveillance system differed from that of the birth cohort, table 4.1. In the birth cohort, pneumonia events were identified in real time. Active surveillance for pneumonia was done by nurses at the six participating clinics who referred birth cohort participants with respiratory symptoms to the research study nurses for assessment, or by directly contacting the study staff through a 24 hour study cell phone. WHO pneumonia case definitions were applied[14]; study nurses were trained in respiratory examination of children, and had regular competency assessments. As the mothers were interviewed frequently through the first year of life, and study staff always enquired about previous respiratory events, it was possible to retrospectively capture pneumonia events occurring at other facilities or outside the area; information was obtained by review of medical records at the admitting facility.[15]

Analysis and statistics

In analysis continuous variables were described as medians (with interquartile ranges, IQR) and categorical variables as proportions with 95 confidence intervals (CI). When using health facility surveillance data, incidence was calculated as the number of pneumonia cases occurring over a continuous 12-month period, using the mid-point population of children under 5 within the catchment area (as reported by the Western Cape Department of Health) as denominator. Incidence rate ratios and risk ratios were calculated with CI based on the Poisson distribution, and proportions were compared with χ^2 tests. All p-values are two-tailed, with α set at 0.05. In comparisons of seasonal incidence, we categorised December to February as summer, March to May as autumn, June to August as winter, and September to November as spring. Ethics approval was obtained from the

University of Cape Town Faculty of Health Sciences Human Research Ethics Committee, HREC REF 401/2009 and REF 651/2013.

4.4 Results

From 1 June 2012 to 30 September 2013, 306 pneumonia events were detected by the surveillance system in children under 1 year of age, of which 56 (18%) were severe pneumonia. The median age of pneumonia diagnosis was 25 weeks, (IQR 15 – 36 weeks). The number of pneumonia cases was lowest in the neonatal period, while the highest burden was in the 3rd month of life, figure 4.1. In 102 pneumonia events (33%), the child was taken directly to the hospital. Of the 204 pneumonia cases identified at the local clinic, 41 (20%) were referred to Paarl hospital. Overall, 52 infants under 1 year (17%) were admitted to hospital. Younger infants were more likely to be admitted to hospital: 21% of infants under 6 months were hospitalized, compared to 13% of infants aged between 6 months and 1 year of age, p=0.008.

There were 1292 infants under 1 year living in the catchment area of the 6 clinics at the mid-point of 2013. For the first full year for which data were available (1 August 2012 till 31 July 2013) the incidence of pneumonia in children in the first year of life was 0.20 episodes/child year (95% CI 0.17 – 0.22), table 4.2.

In the DCHS birth cohort, enrolment of pregnant women began in March 2012, and the first babies were born in May 2012.[12] In the first year of life, 697 children accrued 513 child-years of follow up. There were 141 pneumonia cases, with an incidence of 0.27 episodes per child-year (95% CI 0.23 – 0.32); 32 (23%) of the pneumonia cases were severe, and 55 (39%) were admitted to hospital, table 4.2.[15] 129 cases were identified in real time; 12 cases were identified retrospectively from hospital or clinic records.

The incidence of pneumonia was statistically significantly lower in the surveillance system than in the birth cohort, incidence rate ratio 0.72, 95% CI 0.58 – 0.89. This was most apparent in the first 6 months of life, figure 4.1.

In addition, the proportion of children in the first year of life who were admitted to hospital was statistically significantly lower as measured by the surveillance system (17% vs 39%, p<0.001). Seasonal variation and gender distribution of pneumonia cases were similar between the birth cohort and the surveillance system, with more cases identified in males, and more cases in autumn and winter than in summer and spring, table 4.2. When birth cohort pneumonia events were traced in surveillance system database, 29% had not been identified or reported by the surveillance system.

4.5 Discussion

These results demonstrate a substantial incidence of pneumonia in children under 1 year in this setting, observed in both the facility surveillance system and the birth cohort. This is despite a good primary health care system and comprehensive vaccination program. However incidence of pneumonia as estimated by the surveillance system was somewhat lower than the incidence measured in the birth cohort in the same communities over a similar time period.

There are several reasons why the incidence estimate in the surveillance system was lower than in the birth cohort. Under-reporting of cases at some clinics is possible; some nurses were initially reluctant to complete the surveillance form, and admitted that they forgot about it if they were not visited and reminded. However, as the seasonal variation of pneumonia cases looks similar in the birth cohort, it is unlikely that there was significant decline in pneumonia reporting over the course of the year. Under-detection of pneumonia cases is also possible. Nurses in the clinics were all IMCI-trained, and ongoing training and support was provided, but no formal skills assessment or objective verification of clinical signs was performed. Thus some misdiagnosis of pneumonia cases, and misclassification of severity of disease, is possible. Nurses working in busy clinics may have had less time for accurate completion of the surveillance forms than the study staff on the birth cohort. This may also have contributed to under-detection of severe pneumonia in the surveillance system compared to the birth cohort. Furthermore, children resident in the area who did not attend the local health facility would not have been included in the incidence calculation. There is evidence from a multinational community-based household survey of with respiratory illness that up to 50% of children under 5 years with respiratory symptoms are not taken to a formal health facility.[16]

It is possible that the DCHS birth cohort over-estimated the incidence of pneumonia in these communities, and it is possible that birth cohort participants were more likely to seek care at local clinics than non-participants. However, misclassification bias due to over-diagnosis is unlikely, as the WHO standardised criteria were applied, and birth cohort staff members were well-trained and supervised, and completed regular competency assessments. However, a selection bias may have been introduced if the women who were enrolled in the birth cohort were significantly more at risk for pneumonia than the rest of the local population. This is unlikely, as enrolment for the birth cohort occurred between 20 and 28 weeks gestation, and women were excluded if they had no fixed abode or could not commit to stay in the area. Thus the birth cohort tended to enrol women from comparatively stable social backgrounds. Thus the birth cohort participants may have been at lower risk of pneumonia than many of the other children in these communities.

Accurate estimation of pneumonia incidence is not possible when the person-time at risk is not known. For the surveillance system, the official Department of Health population statistics were used; but if this population was over-estimated, then the estimated incidence would be falsely low. This is a major strength of a birth cohort, where person-time at risk is accurately known for each individual, and all pneumonia events can be recorded, even if identified retrospectively. The DCHS birth cohort required intensive follow up and active pneumonia case detection, which was resource-intense to establish and maintain. It provided an accurate measure of the incidence of pneumonia in this area. The parallel surveillance system was comparatively easier to establish, as clinic staff were already deployed and trained, and all that was required was to request them to complete a single extra data capture form. However, the clinical detail that was available on the surveillance form was limited, and there was no mechanism to control the quality of the data.

This study is unique in that it reports the "real world" pneumonia counts, as diagnosed by local health care workers and converted to incidence estimates using official census data; this incidence estimate is compared to an incidence calculation based on active case finding and accurate assessment of person-time at risk. From these data, it appears that the surveillance system, using routine health care providers, seems to have systematically under-estimated the incidence of pneumonia by about 30% in children under 1 year of age in these communities; and that some of the clinical details and severity assessments also appear to be under-reported, and may be less reliable than those reported in the birth cohort. The lack of detail of clinical signs of pneumonia may make retrospective assessment and re-grading of pneumonia severity especially challenging.

Establishment and maintenance of a clinic-based pneumonia surveillance system is feasible in a peri-urban area in a middle income country, and has provided a valuable estimate of the incidence of childhood pneumonia as measured by health services in this area, and of the age distribution of the pneumonia cases. The results of the pneumonia surveillance system has informed the policies, procedures and resource allocation of the DCHS birth cohort study; the DCHS will continue to follow the children in these communities for 5 years, and will determine the accuracy of the surveillance system estimates in children aged 1-5 years. These data will enable researches to allow for a correction factor in pneumonia incidence calculations, or quantify the potential for under-detection or misclassification that is possible when using routine health facility staff outside of a clinical trial.

4.6 Contributors and acknowledgments

Contributors

HJZ is the principal investigator, and conceived and designed the study, and obtained funding, together with MPN, the lead microbiologist, and LM, who led the epidemiological analyses. HJZ, MPN, and LM provided operational oversight. DMlR was the study clinician and coordinator, analysed preliminary data with supervision from LM, and was the main investigator responsible for interpretation of results and drafting of the manuscript. All authors reviewed, contributed to, and approved the final manuscript.

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Declaration of interests

We declare no competing interests.

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Data sharing agreement

Unpublished datasets will not be made available at this stage

4.7 Strengths and limitations of this study

Strengths

- Direct comparison of 2 different methods for estimating incidence of childhood pneumonia (facility-based pneumonia surveillance, using routine health workers and official census population figures, compared to incidence measured by trained research workers in a birth cohort)
- Gives an approximation of the extent to which the pneumonia surveillance system under-estimated the incidence of pneumonia
- Gives explanation of possible reasons why the surveillance system under-estimated the incidence of pneumonia

Limitations

- Surveillance data reported for relatively short time period: only 16 months (1 full pneumonia season)
- Only infants less than 1 year of age included in analysis as too few events had occurred in older children in the birth cohort to enable comparison; this may limit extrapolation to older children

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4.9 Tables and figures

Table 4.1: Comparison of methods of pneumonia surveillance system and birth cohort

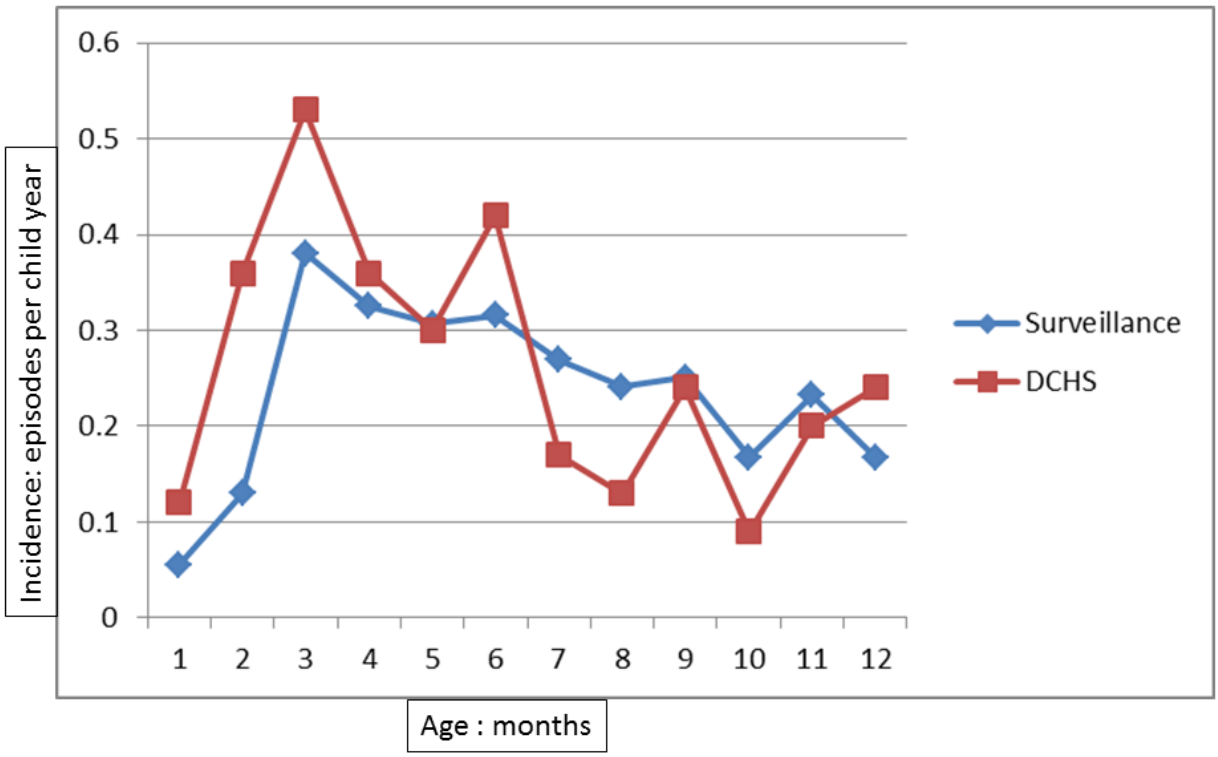
	Facility-based pneumonia surveillance system	**DCHS Birth cohort (le Roux et al, Lancet Glob Health)**
Time period	June 2012 – Sept 2013 (Calendar-year incidence calculation: 1 Sept 2012 – 31 Aug 2013	29 May 2012 – 31 May 2014
Study population	All children < 5 years resident in the catchment area; incidence calculated for children < 1 year of age	Birth cohort participants in first year of life; 697 infants born between 29 May 2012 and 31 May 2014
Estimation of person-time at risk	Estimated 1292 children < 1 year of age from Department of Health population statistics	Calculated for each individual from date of birth till death / disenrollment / first birthday
Method of pneumonia case detection	Clinics: PHC nurse identification of IMCI pneumonia at each facility, and basic data collection form completed. Hospital: record review of children resident in catchment area attending hospital.	Examination by trained study nurse; real-time interview of mother; record review of medical notes Retrospective inclusion of cases: if medical records indicated that they met WHO pneumonia criteria

Table 4.2: Results of pneumonia surveillance system, compared to birth cohort

	Facility-based pneumonia surveillance system	DCHS Birth cohort (le Roux et al Lancet Glob Health)	Comparison (comparing surveillance system to birth cohort)
Incidence: episodes per child year	**0.20 (0.17 – 0.22)**	**0.27 (0.23 – 0.32)**	**IRR 0.72 (0.58 – 0.89; p=0.002)**
Admitted	**52/306 (17%)**	**55/141 (39%)**	**RR 0.44 (0.32 – 0.60; P<0.001)**
Severe pneumonia*	56/306 (18%)	32/141 (23%)	RR 0.81 (0.55 – 1.18; p=0.28)
Male gender	Pneumonia events in males: 194/306 = 63%	Events in males: 97/141 (69%)	RR 0.92 (0.80 – 1.06; p=0.27)
Symptoms:			
Fever	**87/306 (28%)**	**78/141 (55%)**	**RR 0.51 (0.41 – 0.65; p<0.001)**
Wheeze	**93/306 (30%)**	**92/141 (65%)**	**RR 0.47 (0.38 – 0.57; p<0.001)**
Lower chest indrawing	**82/306(27%)**	**81/141 (57%)**	**RR 0.47 (0.37 – 0.59; p<0.001)**
Seasons	(n=254 in one calendar year)	(n=141)	
Summer	35(14%	14 (10%)	p=0.26
Autumn	71 (28%)	39 (28%)	p=0.95
Winter	92(36%)	47 (33%)	p=0.56
Spring	56 (22%)	41 (29%)	p=0.12

IRR = incidence rate ratio
RR = risk ratio
*Criteria for severity as per revised 2014 WHO pneumonia criteria

Figure 4.1: Incidence of pneumonia in the first year of life by age, comparing surveillance system to birth cohort



DCHS: Drakenstein Child Health Study

Chapter 5

Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors

Authors

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5.1 Abstract

Background

Childhood lower respiratory tract infection (LRTI) causes substantial morbidity and under-5 child mortality. The epidemiology of LRTI is changing in low- and middle income countries with expanding access to conjugate vaccines, yet there are few data on the incidence and risk factors for LRTI in these settings.

Methods

A prospective birth cohort enrolled mother-infant pairs in two communities near Cape Town, South Africa. Active surveillance for LRTI was performed for the first 2 years of life over 4 respiratory seasons. Comprehensive data collection of risk factors was done through 2 years of life. World Health Organization definitions were used to classify clinical LRTI and chest x-rays.

Results

From March 2012 to February 2017, 1143 children were enrolled and followed until 2 years of age. 32% of children were exposed to antenatal maternal smoking; 15% were born at low birth weights. 795 LRTI events occurred in 429 children by February 2017; incidence of LRTI was 0.51 episodes per child year (e/cy) in the first year of life and 0.25 e/cy in the second year of life. HIV exposed, uninfected infants (vs. HIV-unexposed infants) were at increased risk of hospitalized LRTI in the first six months of life. In regression models, male sex, low birth weight and maternal smoking were independent risk factors for both ambulatory and hospitalized LRTI; delayed or incomplete vaccination was associated with hospitalized LRTI.

Conclusions

LRTI incidence was high in the first year of life, with substantial morbidity. Strategies to ameliorate harmful exposures are needed to reduce LRTI burden in vulnerable populations.

5.2 Introduction

Childhood lower respiratory tract infections (LRTI) cause over 700 000 deaths in children under-five years (U5) annually. This is a substantial decrease from 1.7 million LRTI-associated U5 deaths in 1990, reflecting decreased LRTI incidence.[1] These improvements in childhood LRTI burden and mortality have largely been due to improved living conditions, childhood nutrition, expanding access to childhood vaccines, including conjugate vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib).[2] Decreased bacterial LRTI has resulted in proportional increase in viral or mixed infective LRTI,[3] which may require different prevention and management strategies. Further reduction of the residual burden of childhood LRTI, especially severe and hospitalized LRTI, requires better understanding of its changing epidemiology and risk factors, in order to strengthen interventions.[4]

Young children, especially under 6 months of age, remain at greatest risk for severe LRTI.[5,6] Prematurity predicts severe viral LRTI[7] and mortality in both low income and high income countries (HIC).[8] However, effects of other risk factors may not be constant across settings: lack of exclusive breastfeeding has larger effect in low- and middle-income countries (LMIC; 2.7 times increased risk of severe LRTI) compared to HIC (1.3 times increased risk).[9] Risk factors like severe malnutrition are rare in HIC, but common in LMIC. Excess risk associated with HIV exposure may be ameliorated by maternal antiretroviral therapy and improved breastfeeding,[10,11] or may have an effect only in early infancy, but there are no longitudinal data investigating this.

Accurate measurement of population-based LRTI incidence in young children in LMIC is challenging; birth cohorts with active LRTI surveillance provide unique opportunities for direct measurement of incidence, severity and risk factors, including variations over seasons. This study aimed to investigate incidence, severity and age-specific risk factors of LRTI among children enrolled in an African birth cohort, the Drakenstein Child Health Study (DCHS) followed until 24 months of age, over 4 respiratory seasons (2012-2017).

5.3 Methods

Study design and population

The DCHS is a birth cohort outside Cape Town, South Africa. Detailed description of the cohort is published elsewhere.[12] Briefly, pregnant women (20-28 weeks' gestation) attending antenatal care at one of 2 clinics were recruited and followed through pregnancy, delivery and with their children for 2 years. These two clinics serve 2 communities with different cultural profiles, reflecting South Africa's political history of racial segregation. One community was historically restricted to individuals of mixed ancestry (Newman); the other to individuals of black African ancestry (Mbekweni). Both communities are of low socio-economic status (SES) with high unemployment and HIV prevalence. University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC 401/2009; 651/2013) provided ethical approval. Mothers provided written informed consent at enrolment, with annual renewal.

Childhood vaccinations followed national schedules: Bacille Calmette Guerin (BCG) at birth; 13-valent pneumococcal conjugate vaccine (PCV13) (6 weeks, 14 weeks, 9 months); hexavalent vaccine (including acellular pertussis and Hib) (6, 10, 14 weeks, and 18 months); and measles vaccine (9 and 18 months). Guidelines for prevention of mother-to-child transmission of HIV (PMTCT) changed during the study period. Before 2014, most HIV-infected women received only nevirapine (NVP) and zidovudine (ZDV); those with CD4 cell counts < 350 cells/mm^3 initiated triple antiretroviral therapy (ART). From 2014, ART was initiated without CD4 restriction. HIV-exposed infants were tested with HIV-DNA PCR (Cobas Ampliprep/Cobas Taqman HIV-1, Roche Diagnostics Systems, Inc., Branchburg, NJ) between 6 and 10 weeks, and repeated if hospitalized. Repeat testing occurred at 9- and 18-months using age-appropriate tests according to local guidelines. HIV-exposed infants were given co-trimoxazole prophylaxis from 6 weeks until breastfeeding discontinuation.

Study procedures

The primary outcome was LRTI incidence, with differentiation by severity (WHO-severe or hospitalization). Study staff, based at both clinics and the single regional hospital, performed LRTI surveillance using active case finding.[13] LRTI was diagnosed according to revised WHO guidelines when a child had cough or difficulty breathing, with either lower chest wall indrawing (LCWI) or age-appropriate tachypnoea ($\geq$ 50 breaths/minute if 2-12 months, $\geq$40 breaths/minute if $\geq$12 months).[14] "Severe" LRTI was diagnosed in children <2 months with tachypnoea $\geq$ 60 breaths/minute or LCWI; or in children of any age with danger signs (cyanosed, unable to drink, seizures, or decreased level of consciousness).[14] In children with wheezing, LRTI was not diagnosed if tachypnoea and LCWI resolved following inhaled bronchodilator. LRTI events were diagnosed at the hospital or a clinic;

severe cases seen at a clinic were referred to the hospital. Indications for hospitalization included hypoxia (oxygen saturation <92% on room air), or poor social circumstances making ambulatory treatment unfeasible. Decision to hospitalize was made by treating clinicians not study staff. Events occurring > 14 days following LRTI were considered new-onset LRTI. Chest X-rays were taken when hospitalized for LRTI, and read by 2 independent doctors trained in WHO-standardized chest X-ray reporting.[15] A third reader, blinded to previous readings, resolved discordant results. Risk factors of interest (birth weight and gestation, HIV exposure, socio-economic status, exposure to environmental tobacco smoke (ETS)) were recorded for all participants. Trained study staff administered structured interviews regarding symptoms and household / environmental exposures at enrolment, after delivery, at scheduled follow-up visits, and when diagnosed with LRTI. Smoking during pregnancy was classified by antenatal urine cotinine: non-smoker (< 10 ng/mL), passive smoker (10–499 ng/mL) or active smoker (≥500 ng/mL).[16]

Statistical analysis

Predictors of ambulatory and hospitalized LRTI were explored with Poisson regression using generalized estimating equations clustered on mother-infant pairs.[17] Results are presented as unadjusted and adjusted incidence rate ratios (IRR). Follow-up was censored at 2 years of age, last visit seen, or 28 February 2017. Analyses were stratified by child age to account for potential effect modification by age, with adjustment for enrolment clinic throughout. Due to markedly increased incidence of LRTI in HIV infection, 2 HIV-infected children were excluded from Poisson regression after sensitivity analysis indicated large changes in IRR estimates of several other risk factors. Final model selection was based on parsimony and lowest Akaike's Information Criterion (AIC).[18] Population attributable risks (PAR)[19] of potentially modifiable risk factors for LRTI were calculated, including for maternal smoking. Data were analysed using Stata version 11 (College Station, Texas, USA).

5.4 Results

Between March 2012 and March 2015, 1137 pregnant women were enrolled, delivering 1143 live-born infants (4 sets of twins, 1 of triplets), figure 5.1. Overall, 849 children (74%) had completed 2 years follow-up by analysis censoring (February 2017); 153 children (13%) were disenrolled before age 2 years (median disenrollment age 6 months; reasons were predominantly moving out of area (56, 37%) and inability to contact mothers (35, 23%). Median follow-up was 24 (inter-quartile range (IQR) 23.6 – 24) months, with 2043 child-years accrued in total.

Table 5.1 describes mother-child pairs. Household ETS was common: 82% of children were exposed in the first 6 months of life, either by their own mothers or by other family members. Antenatal

smoking was more common in mixed ancestry (53%) than in black African households (15%). HIV was more common in African women (36%) than in those of mixed ancestry (3%). Coverage of primary series of PCV13 and hexavalent vaccine were excellent (92%).

There were 247 (22%) HIV-exposed uninfected (HEU) children; 2 HIV-infected children commenced ART. Most women (1016, 89%) initiated breastfeeding but duration of exclusive breastfeeding was short (median 1.8 months, IQR 0.9-3.7). By 6 months, only 86 (8%) babies were exclusively breastfed and 76 (6%) partially breastfed (breast and formula milk). HIV-exposed babies were less likely to initiate any breastfeeding (140/249, 56%), than HIV-unexposed babies (875/893, 98%), p<0.0001. (Supplementary table 5.1)

Clinical characteristics of LRTI events

There were 795 LRTIs in 429 children in the first 2 years of life. Some children had multiple LRTIs; by 2 years, 38% of the cohort had had at least 1 LRTI. Young children had the highest burden: 96 (55%) hospitalizations and 116 (66%) WHO-severe LRTI occurred in children under 6 months. Of all LRTI, 176 (22%) were WHO-severe, of which 92/176 (52%) required hospitalization. Associated comorbidities and non-LRTI reasons for hospitalization are shown in supplementary table 5.2. Median age at hospitalized LRTI was 4.4 months (IQR 1.8 – 11.0), compared to 7.3 months (IQR 4.0 – 14.2) for ambulatory LRTI, p<0.0001.(Table 5.2) There were no significant differences between ambulatory and hospitalized events by enrolment clinic, socio-economic status, or season. Preceding coryza and upper respiratory tract symptoms (82%), history of fever (66%), and wheezing (45%) were common.

Of 174 hospitalized LRTI events, 162 (93%) had interpretable chest X-rays. Radiological abnormality was reported in 124 (78%); 64 (40%) had primary end-point consolidation (PEPC) and 62 (38%) had other infiltrates. Children with radiological abnormality were equally likely to be hypoxic (32/126, 25%) as children without radiological changes (10/36, 28%, p=0.77). Continuous positive airway pressure or intubation and mechanical ventilation was needed in 14 children (8%). There were 3 deaths (case fatality 1.7% of hospitalized, 0.4% overall).

Incidence of LRTI

Incidence of LRTI in the first year of life was 0.51 episodes per child year (e/cy), decreasing to 0.25 e/cy in the second year. Incidence of hospitalized LRTI in the first year of life was 0.13 e/cy and in the second year, 0.04 e/cy. (Table 5.3). There were more LRTI cases in 2014-2015 than in 2012-2013; incidence of hospitalized LRTI <1 year was 0.10 e/cy (95% CI 0.08 – 0.14) in the early time period, and 0.15 e/cy (95% CI 0.12 – 0.18) in the later period.

Risk factors for LRTI

Hospitalized: In unadjusted Poisson regression, hospitalized LRTI in the first 6 months of life was associated with maternal smoking, male sex, delayed or missed vaccinations, preterm delivery (PTD), and low birth weight (<2500g, LBW) as well as maternal HIV infection and household crowding. Maternal smoking, delayed or missed vaccinations, LBW or PTD remained significant risk factors between 6 and 12 months, but not after 12 months. (Table 5.4).

Ambulatory: Throughout the first 2 years, ambulatory LRTI was strongly associated with maternal smoking; male sex and lower socio-economic status were significant risk factors in the first year of life. PTD and LBW were significant only after 6 months of age; HIV exposure or delayed or missed vaccinations were not associated with ambulatory LRTI. (Table 5.4).

HIV and breastfeeding

HIV-exposed uninfected (HEU) infants <6 months had increased incidence of hospitalized LRTI (IRR 1.99, 95% CI 1.11 – 3.54) compared to HIV-unexposed (HU) infants; there was no effect of HIV exposure beyond 6 months of age.(Table 5.4) In addition, HEU infants born to mothers who received triple ART in pregnancy had lower incidence of hospitalized LRTI in the first year of life (0.14 e/cy) compared to HEU infants whose mothers only received dual prophylaxis (NVP+ZDV) PMTCT (0.28 e/cy; IRR 0.49, 95% CI 0.26 – 0.96). Effects of breastfeeding varied by HIV exposure status: the 11/886 (1.2%) HU infants who never breastfed had higher incidence of hospitalized LRTI < 6 months compared to HU infants who ever breastfed (IRR 7.46, 95% CI 2.83 – 19.7). However, among HEU infants <6 months, the 99/239 (41%) who never breastfed had similar incidence of hospitalized LRTI compared to breastfed HEU infants, (IRR 1.19, 95% CI 0.51 – 2.74).

Adjusted Poisson model and population attributable risk

In adjusted Poisson regression (controlling for age and enrolment clinic), male sex, LBW, delayed or missed vaccinations and maternal smoking remained significant predictors of both ambulatory and hospitalized LRTI.(Table 5.5) The PAR of antenatal maternal smoking for LRTI (tobacco-unexposed children vs children of active or passive smokers), was 13.8% (95% CI -0.01 to 27.3%); PAR for low birth weight was 9.2% (95% CI 1.5% to 16.1%).

5.5 Discussion

This unique birth cohort provides important longitudinal data on incidence, severity and risk factors for LRTI in a well-vaccinated population, with almost no HIV-infected children, through the first 2 years of life and extending across 4 respiratory seasons. We describe LRTI incidence in the second year of life, with lower overall incidence and increased proportion of ambulatory cases compared to infants < 1 year. This represents an appreciable burden of LRTI: in South Africa, with an annual birth cohort of 1.2 million,[20] translating to 48 000 LRTI hospitalizations in the second year of life, adding substantial burden and costs to health systems.

Incidence of LRTI in infants under 1 year of age was much higher than previously described.[21] As case detection methods remained constant through the study period, the observed increased incidence is most likely due to severe pneumonia seasons in 2014 and 2015. This inter-year variation in seasonal pneumonia severity underscores the importance of multi-year birth cohorts with extended recruitment and follow-up. In addition to high LRTI incidence in infancy, our study highlights vulnerability of infants and young children to LRTI; high prevalence of risk factors such as ETS, low birth weight and maternal HIV; and persistence of LRTI burden into the second year of life.

In-hospital case fatality was low (<2%) despite severity of disease, prevalence of radiological abnormality in 78% of hospitalized cases and hypoxia in 25%. This is lower than in the multi-site Pneumonia Etiology Research and Child Health (PERCH) study: of 3587 children admitted with severe LRTI, 54% had radiological abnormality, 36% were hypoxic, and 6% died.[22] Our estimates are also lower than a report of children with severe LRTI in Botswana, where 79% had radiological abnormality, 38% were hypoxic and 5% died.[23] Our low case fatality may reflect good access to care, including access to intensive care and mechanical ventilation. Our cohort also achieved high vaccine coverage, including PCV and HibCV; had good nutritional status; and low prevalence of HIV infection in children, factors that may have contributed to low case fatality.

Antenatal maternal smoking was a consistent modifiable risk factor for both ambulatory and hospitalized LRTI throughout the first 2 years. The PAR for LRTI implies that 13.8% of LRTI was due to antenatal maternal smoking. Although higher than reported globally[1], this may still be an under-estimate, as measurement of the intensity of postnatal ETS exposure from self-reported questionnaires was difficult; accurate antenatal biomarkers like maternal urine cotinine may not capture the additive impact of postnatal ETS exposure.

Preterm and low birth weight children were at high risk for LRTI throughout early childhood, with younger infants more likely to require hospitalization, consistent with previous studies.[2] PTD and

LBW were significant risk factors for ambulatory LRTI after 6 months of age, and through the second year of life. Children with delayed or missed vaccinations had increased incidence of LRTI, even after adjusting for other risk factors. This may reflect immunological susceptibility; however, delayed vaccinations may also indicate social vulnerability, or be a marker of other unmeasured risk factors.[24,25]

HEU infants had 2-fold increased incidence of hospitalized LRTI compared to HU infants, as previously described.[11,26] A novel finding was that this was limited to the first 6 months of life, possibly due to impaired maternal transplacental antibody[27] or transient innate or adaptive immune effects in HEU.[28,29] This raises questions about optimal prevention strategies, including possible co-trimoxazole prophylaxis in HEU for 6 months. HEU born to mothers using simple PMTCT regimens had higher incidence of hospitalized LRTI than infants born to mothers using triple ART in pregnancy. This is consistent with evidence that maternal triple ART is associated with decreased all-cause child mortality at 24 months.[30] Future estimates of population effects of HIV exposure on childhood LRTI should adjust for maternal ART regimens.

Globally, breastfeeding is associated with decreased LRTI hospitalization for 2 years.[31] We observed lower hospitalized LRTI incidence among the 99% of HU infants <6 months who were breastfed compared to 1% of HU infants who never breastfed; however there is possibility of unmeasured confounding among those who never breastfed. Short duration of protective effect is likely due to overall short duration of breastfeeding. Differential effect of breastfeeding on LRTI incidence by HIV exposure status has been described in 2 previous South African cohorts. In a case control study in Soweto, breastfeeding was protective against "presumed bacterial pneumonia" among HU, but not HEU children;[32] in a Cape Town cohort, breastfeeding among HEU infants was not protective against hospitalization.[33] By contrast, a cohort of breastfed Kenyan HEU infants had 47% decreased risk of LRTI compared to non-breastfed HEU infants.[34] It is possible that in South African cohorts, (well-vaccinated, receiving cotrimoxazole prophylaxis, well-nourished, with good access to care), breastfeeding among HEU did not confer the same protection against LRTI as in Kenya.

A major strength of this study is the long follow-up, including several respiratory seasons. Longitudinal birth cohorts are rare in LMICs; cross-sectional analyses of LRTI do not have accurate measurement of pre-existing risk factors, but rely on recall.[35,36] With this study design we could prospectively measure risk factors for LRTI at different time points whilst allowing for inter-year variation in background risk. Limitations include low specificity of WHO clinical case definitions, alongside possibility of LRTI overdiagnosis due to heightened awareness of staff and mothers about respiratory symptoms. Nonetheless, LRTI signs were verified by study staff and a high proportion required hospitalization of which most had radiological changes. Some cases of LRTI may have been

missed; however this is unlikely given strong surveillance systems and high cohort retention. Another limitation is lack of etiology data. Although microbiologic data has been reported,[37] ascribing etiology can be complex and is beyond the scope of this paper. A further limitation is potential for interobserver variability in radiological interpretation of LRTI; however we used the same 3 readers, and standardised WHO reporting form. Moreover, interobserver variability has been reported to be high for end-point consolidation.[38]

In conclusion, we report high incidence of clinical and radiological LRTI in the first 2 years of life, with low case fatality. There remains an appreciable burden, especially of ambulatory disease, in the 2nd year. Low birth weight, delayed / missed vaccinations and maternal smoking were strong risk factors for LRTI. HEU were at higher risk of hospitalized LRTI only in the first 6 months of life. Strategies to identify incompletely vaccinated children and prevent harmful exposures including ETS must be strengthened, and new strategies for protecting vulnerable children are needed to reduce the burden of LRTI.

5.6 Contributors and acknowledgments

Contributors

DLR was the study clinician and coordinator, analysed data with supervision from LM, and was the main investigator responsible for interpretation of results and drafting of the manuscript. HJZ is the principal investigator, and conceived and designed the study, and obtained funding, together with MPN, the lead microbiologist, and LM, who led the epidemiological analyses. HJZ, MPN, and LM provided operational oversight. AV obtained funding for and led analysis of environmental tobacco smoke. JAMS was study clinician and coordinator and read and reviewed xrays. EvD read and reviewed xrays and advised on clinical assessments. All authors reviewed, contributed to, and approved the final manuscript.

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Declaration of interests

We declare no competing interests.

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5.8 Tables and figures

Table 5.1: Baseline characteristics of 1143 mother-infant pairs enrolled into the birth cohort at two sites

	Mbekweni	TC Newman	Total	P Value
Maternal characteristics	(n=626 mothers)	(n=511 mothers)	1137	
Formal housing, n(%)	353 (56)	362 (71%)	715 (63%)	<0.0001
Household crowding:				
4 or fewer people, n(%)	263 (42%)	118 (23%)	381 (34%)	<0.0001
5 or more, n(%)	362 (58%)	391 (77%)	753 (66%)	
Maternal smoking, (by antenatal urine cotinine) n(%)				
Non smoker (Cotinine <10ng/ml)	195 (34%)	56 (12%)	251 (24%)	
Passive smoker (Cotinine 10-499 ng/ml)	291 (51%)	173 (36%)	464 (44%)	<0.0001
Active smoker (Cotinine ≥500 ng/ml)	89 (15%)	254 (53%)	343 (32%)	
Infant characteristics	(n=632 children)	(n=511 children)	1143	
Male, n(%)	312 (49%)	278 (54%)	590 (52%)	0.09
Pre term (<37 weeks), n(%)	108 (17%)	82 (16%)	190 (17%)	0.60
Low birth weight (<2500g), n(%)	78 (12%)	96 (19%)	174 (15%)	0.003
HIV status: HIV unexposed, n(%)	400 (63%)	494 (97%)	894 (78%)	<0.0001
HIV exposed, uninfected, n(%)	230 (36%)	17 (3%)	247 (22%)	
HIV infected, n(%)	2 (0.3%)	0	2 (0.2%)	
Breastfeeding: Never breast fed, n(%)	99 (16%)	11 (2%)	110 (10%)	<0.0001
Breastfed less than 6 months, n(%)	421 (67%)	433 (85%)	854 (75%)	
Breastfed at least 6 months, n(%)	97 (15%)	65 (13%)	162 (14%)	
Unknown	15 (2%)	2 (0.4%)	17 (1.5%)	
EPI vaccine coverage (n=871)				
All doses given, on time, n(%)	437 (92%)	360 (91%)	797 (92%)	0.43
All doses given , some doses late, n(%)	34 (7%)	36 (9%)	70 (8%)	
At least 1 missing dose, n(%)	3 (0.6%)	1 (0.25%)	4 (0.5%)	

Table 5.2: Comparison of ambulatory and hospitalized LRTI events

	Ambulatory (621 events)	**Hospitalized (174 events)**	**P value**
Number of children	369	133	
Enrolment clinic: Mbekweni, n(%) TC Newman, n(%)	366 (59%) 255 (41%)	95 (53%) 79 (47%)	 0.31
Year of study: 2012 **2013** **2014** **2015** **2016**	36 (6%) 83 (13%) 238 (38%) 213 (34%) 51 (8%)	16 (9%) 47 (16%) 62 (37%) 43 25%) 6 (3%)	**<0.0001**
Season: Autumn, n(%) Winter, n(%) Spring, n(%) Summer, n(%)	173 (28%) 205 (33%) 164 (26%) 79 (13%)	46 (26%) 69 (40%) 37 (21%) 22 (13%)	0.35
Mother active smoker in pregnancy[1]	231 (39%)	69 (43%)	0.42
Males, n(%)	376 (61%)	116 (67%)	0.14
Age month, median (IQR)	7.3 (4.0 – 14.2)	4.4 (1.8 – 11.0)	**<0.0001**
Under 6 months, n(%) 6 -12 months, n(%) Over 12 months, n(%)	266 (43%) 134 (22%) 221 (36%)	96 (55%) 42 (24%) 36 (21%)	**<0.0001**
Pre term: <37 weeks, n(%)	126 (20%)	52 (30%)	**0.008**
Low birth weight: <2500g, n(%)	130 (21%)	49 (28%)	**0.046**
HIV unexposed HIV exposed, uninfected, n(%) HIV infected, n(%)	469 (76%) 151 (24%) 1 (0.2%)	125 (72%) 46 (26%) 3 (2%)	**0.03**
Weight-for-length Z score, at time of LRTI	0.65 (-0.22; 1.7)	0.6 (-0.84; 1.72)	0.13
Duration of exclusive breastfeeding (months)	1.84 (0.92 – 3.22)	1.84 (0.92 – 4.0)	0.81
Preceding diarrhoea, n(%)	66 (11%)	37 (21%)	**<0.0001**
Respiratory rate, median (IQR)	53 (46 to 59)	62 (56 to 69)	**<0.0001**
Lower chest indrawing, n(%)	383 (63%)	150 (86%)	**<0.0001**
Wheeze at the time of LRTI), n(%)	266 (43%)	92 (53%)	**0.02**
Oxygen saturation, median (IQR)	98 (96 to 99)	94 (89 to 96)	**<0.0001**
Hypoxia (O2 sats <92), n(%)	6 (1%)	43 (25%)	**<0.0001**
Chest xray findings (WHO classification) No consolidation / infiltrate, n(%) Other consolidation / infiltrate, n(%) Primary end point consolidation or pleural effusion, n(%)		 36 (22%) 62 (38%) 64 (40%)	
Ventilation received Continuous positive airway pressure Mechanical ventilation		 6 (3%) 8 (5%)	

1. Urine cotinine $\geq$ 500ng/ml

Table 5.3: Incidence rates of ambulatory, hospitalized and WHO severe LRTI in the first 2 years of life

	Ambulatory LRTI e/cy	**Hospitalized LRTI e/cy**	**WHO severe LRTI e/cy**	**All clinical LRTI e/cy (95% CI)**
Under 1 year (person-time: 1090.18 child-years)	(n=415) 0.38 (0.24 – 0.42)	(n=139) 0.13 (0.11 – 0.15)	(n=137) 0.13 (0.11 – 0.15)	(n=554) 0.51 (0.47 – 0.55)
1-2 years (person-time: 951.45 child-years)	(n=206) 0.22 (0.19 – 0.25)	(n=35) 0.04 (0.03 – 0.05)	(n=40) 0.04 (0.03 – 0.06)	(n=241) 0.25 (0.22 – 0.29)
Total (person-time: 2041.63 child-years)	(n=621) 0.30 (0.28 – 0.33)	(n=174) 0.09 (0.07 – 0.10)	(n=177) 0.09 (0.07 – 0.10)	**(n=795)** 0.39 (0.36 – 0.42)

e/cy: Episodes per child year

Table 5.4: Risk factors, as incidence rate ratios for ambulatory and hospitalized LRTI for 1141 HIV-uninfected children in the first 2 years of life, from Poisson regression

		Ambulatory			Hospitalized	
	Under 6 months	6 – 12 months	Over 12 months	Under 6 months	6 – 12 months	Over 12 months
Mother active smoker in pregnancy[1]	**1.14 (0.98 – 1.34)**	**1.50 (1.24 – 1.81)**	**1.21 (1.01 – 1.44)**	**1.35 (1.07 – 1.72)**	**1.67 (1.15 – 2.42)**	0.80 (0.51 – 1.24)
SES quartile: Highest	1	1	1	1	1	1
Moderate-high	1.41 (0.92 – 2.18)	1.14 (0.64 – 2.03)	0.93 (0.57 – 1.51)	1.36 (0.72 – 2.57)	1.33 (0.51 – 3.73)	2.77 (0.89 – 8.64)
Moderate-low	**1.71 (1.15 – 2.55)**	**2.07 (1.26 – 3.42)**	1.54 (0.98 – 2.42)	1.36 (0.72 – 2.57)	1.53 (0.58 – 4.08)	1.53 (0.44 – 5.33)
Lowest	1.25 (0.81 – 1.93)	1.66 (0.96 – 2.87)	**1.69 (1.07 – 2.66)**	1.43 (0.75 – 2.73)	1.70 (0.60 – 4.80)	2.25 (0.63 – 8.09)
Household size:						
4 or fewer people	1	1	1	1	1	1
5 or more	0.87 (0.65 – 1.17)	0.85 (0.59 – 1.24)	1.10 (0.79 – 1.55)	**2.36 (1.34 – 4.13)**	1.34 (0.69 – 2.60)	1.22 (0.55 – 2.73)
Male (compared to female)	**1.65 (1.25 – 2.18)**	**1.54 (1.07 – 2.20)**	1.22 (0.89 – 1.67)	**1.82 (1.15 – 2.87)**	1.77 (0.93 – 3.36)	2.10 (0.99 – 4.48)
Low birth weight	1.10 (0.76 – 1.60)	**2.01 (1.35 – 3.01)**	**1.88 (1.27 – 2.77)**	**2.03 (1.24 – 3.33)**	**2.52 (1.13 – 5.63)**	2.03 (0.80 – 5.15)
Pre-term	1.00 (0.71 – 1.42)	**1.63 (1.09 – 2.43)**	**1.57 (1.07 – 2.30)**	**2.48 (1.55 – 3.94)**	**2.35 (1.08 – 5.08)**	1.09 (0.40 – 2.95)
HIV exposed	1.32 (0.95 – 1.84)	0.98 (0.61 – 1.57)	0.91 (0.60 – 1.38)	**1.99 (1.11 – 3.54)**	1.26 (0.44 – 3.60)	0.83 (0.21 – 2.20)
Wasting[2]	0.94 (0.70 – 1.27)	1.20 (0.53 – 2.69)	1.23 (0.52 – 3.42)	0.75 (0.45 – 1.25)	1.76 (0.45 – 6.85)	*unable to calculate
All vaccine doses on time	1	1	1	1	**1**	1
Some doses late or missed	1.08 (0.63 – 1.84)	1.23 (0.71 – 2.15)	1.41 (0.77 – 2.57)	**2.31 (1.21 – 4.41)**	**3.44 (1.34 – 8.86)**	1.56 (0.48 – 5.04)
Season: Summer	1	1	1	1	1	1
Spring	**1.60 (1.08 – 2.37)**	1.56 (0.91 – 2.66)	1.08 (0.68 – 1.73)	1.48 (0.68 – 3.21)	1.33 (0.57 – 3.14)	1.93 (0.64 – 5.85)
Autumn	**1.72 (1.16 – 2.55)**	**2.31 (1.37 – 3.87)**	**2.09 (1.41 – 3.09)**	**2.61 (1.31 – 5.18)**	1.71 (0.67 – 4.32)	2.30 0.77 – 6.82)
Winter	**2.05 (1.37 – 3.06)**	**2.04 (1.20 – 3.44)**	**2.05 (1.37 – 3.07)**	**3.14 (1.61 – 6.12)**	2.23 (0.90 – 5.53)	1.74 (0.56 – 5.43)

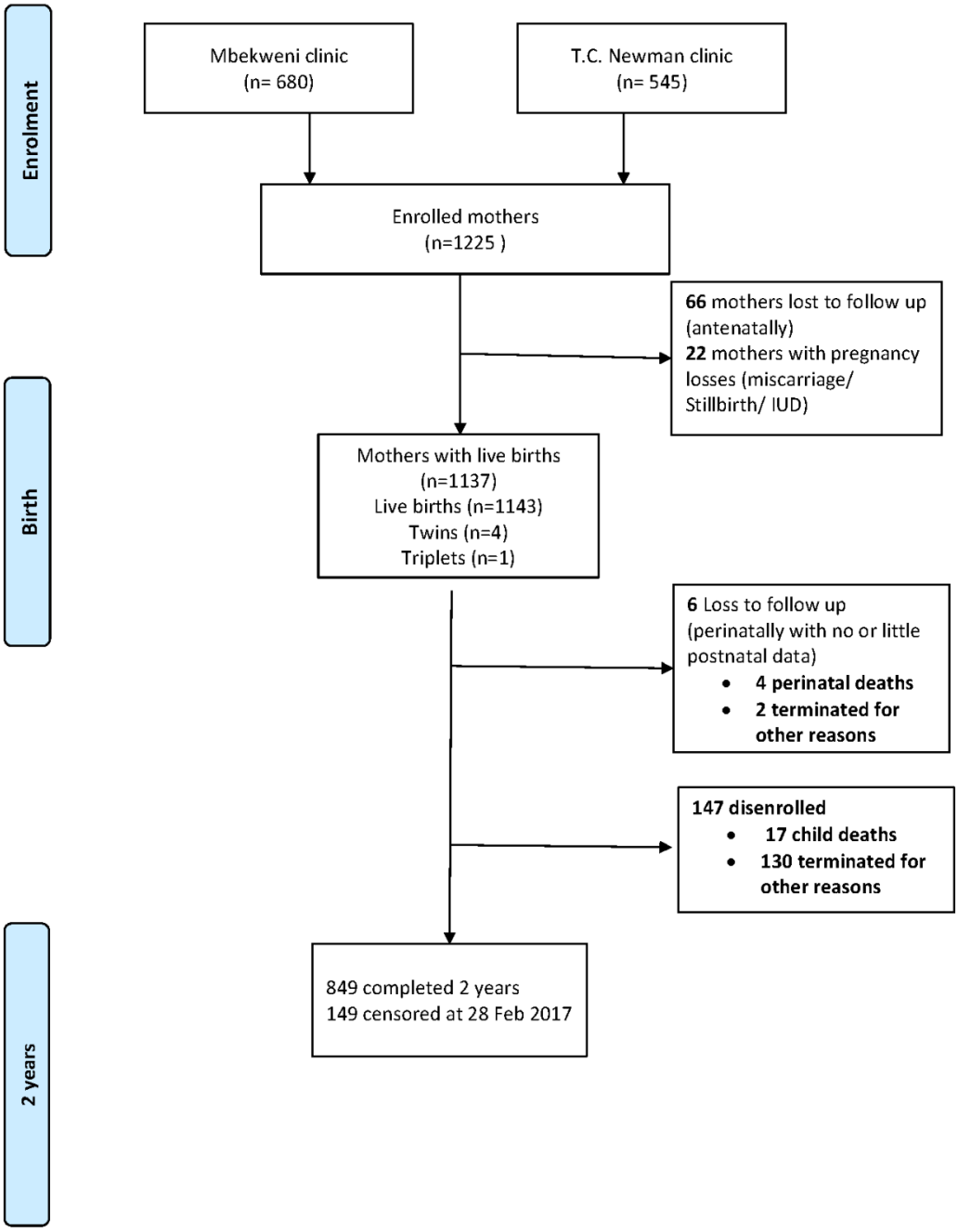
1. Urine cotinine >500ng/ml
2. Weight for height Z-score < -2

Table 5.5: Risk factors for ambulatory and hospitalized LRTI for 1141 HIV-uninfected children in the first 2 years of life: adjusted multivariable model

	Ambulatory LRTI Adjusted[1]IRR and 95% CI	**Hospitalized LRTI Adjusted[1]IRR and 95% CI**
Age category: Under **6** months 6-12 months Over 12 months	**2.17 (1.75 – 2.68)** **1.34 (1.06 – 1.69)** **1**	**4.87 (3.12 – 7.63)** **2.12 (1.29 – 2.87)** **1**
Male sex	**1.53 (1.20 – 1.96)**	**1.88 (1.23 – 2.87)**
Low birth weight	**1.53 (1.12 – 2.08)**	**1.79 (1.09 –2.94)**
Mother active smoker in pregnancy[2]	**1.53 (1.20 – 1.97)**	**1.63 (1.05 – 2.94)**
Delayed or missing vaccinations	1.03 (0.91 – 1.17)	**1.31 (1.09 – 1.58)**

1. IRR: Incidence rate ratio. Adjusted for enrolment clinic, age, sex, low birth weight, maternal smoking, delayed / missing vaccinations
2. Urine cotinine >500ng/ml

Figure 5.1: Flow chart of participants through the Drakenstein Child Health Study



Supplementary table 5.1: HIV exposure, use of antenatal antiretroviral therapy, and association with risk factors for LRTI, among 1141 HIV-uninfected children

	HIV Unexposed (n=894)	HIV exposed, mother received triple ART[1] (n=180)	HIV exposed, limited ART[2] (n=69)	P value
Pre term delivery	142 (16%)	34 (19%)	13 (20%)	0.52
Low birth weight	137 (15%)	24 (13%)	12 (18%)	0.70
Never breast fed, n(%) **Breastfed less than 6 months, n(%)** **Breastfed at least 6 months, n(%)** **Unknown**	11 (1%) 754 (84%) 122 (14%) 7 (1%)	71 (39%) 73 (41%) 29 (16%) 7 (4%)	28 (41%) 27 (39%) 11 (16%) 3 (4%)	<0.0001
Duration exclusive breast feeding, median (IQR)	1.84 (0.91; 3.0)	2.76 (0.92; 5.52)	2.76 (0.45; 5.0)	
Weight for length Z score: **Birth (n=1143 at birth)** **6 months (n=1070)** **12 months (n=1018)** **24 months (n=861)**	 -1.09 (-2.32; 0.2) 0.70 (-0.41; 1.56) 0.33 (-0.50; 1.30) 0.28 (-0.49; 1.08)	 -1.15 (-1.99; 0.38) 0.96 (0.1; 1.67) 0.81 (-0.40; 1.47) 0.38 (-0.31; 1.47)	 -0.23 (-2.36; 0.81) 1.20 (0.16; 2.04) 0.19 (-0.56; 1.40) 0.45 (-0.06; 1.67)	
Weight for length Z score < -2 **Birth (n=1143 at birth)** **6 months (n=1070)** **12 months (n=1018)** **24 months (n=861)**	 266 /894 (30%) 20/716 (3%) 8 / 301 (3%) 11 / 465 (2%)	 43/180 (24%) 5/145 (3%) 0 / 60 (0%) 0/69 (0%)	 18/ 64 (28%) 3/55 (5%) 1/20 (5%) 1/32 (3%)	 0.29 0.50 0.34 0.41

1. Triple ART: 3 agent, life-long antiretroviral therapy
2. Limited ART: short term antenatal therapy with nevirapine or zidovudine, for prevention of mother-to-child transmission of HIV

Supplementary table 5.2: Co-morbidities diagnosed and procedures performed in 174 hospitalized LRTI events

	Number of children	Age in weeks at LRTI admission (median, IQR)
Comorbidity		
Documented hypoxia or oxygen requirement	43	14 (7 – 51)
Age < 2 months	47	6 (4 – 8)
Diarrhoea	40	42 (8 – 44)
Growth faltering	14	34 (21 – 55)
Newly diagnosed tuberculosis	12	29 (19 – 48)
Severe anaemia: Hb<8	8	14 (7 – 24)
Presumed *Pneumocystis jirovecii* pneumonia	7	13 (5 – 22)
Congenital cardiac lesion (5 events in 4 children)	5	12 (10 – 28)
Seizures (4 events in 2 children)	4	48; 74; 81; 90 weeks
HIV infection (3 events in 1 child)	3	12, 15, 52 weeks
Cerebral palsy	2	22; 51 weeks
Urinary tract infection	2	5; 39 weeks
Tonsillitis	2	59; 82 weeks
Procedures and investigations		
Lumbar puncture	15	6 (4 – 11)
IPPV	8	6 (4 – 18)
CPAP	6	10 (4 – 17)
Contrast fluoroscopy swallow	3	22; 50; 35 weeks
CT chest	1	21 weeks
CT brain	1	75 weeks

IPPV: Intermittent positive pressure ventilation
CPAP: Continuous positive airways pressure
CT: computed tomography

Chapter 6

Factors associated with serious outcomes of pneumonia among children in a birth cohort in South Africa

Authors

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6.1 Abstract

Background

Child hospitalization for pneumonia remains common, and pneumonia is a major cause of child mortality. Early identification of clinical factors associated with serious outcomes may help target risk-mitigation strategies.

Methods

Pneumonia cases occurring in the Drakenstein Child Health Study, a prospective birth cohort outside Cape Town, South Africa were analysed, and factors associated with serious outcomes of pneumonia were identified. Pregnant women were enrolled antenatally, followed through pregnancy, and mother-child pairs from birth to 2 years. Active surveillance for pneumonia was done. Children hospitalized with pneumonia had chest radiography and blood drawn for inflammatory markers; course, outcome and duration of hospitalization were investigated. Serious outcomes were defined as in-hospital mortality or admission to intensive care unit (ICU). Prolonged hospitalization was also explored as a proxy for severity. Features associated with serious outcomes or prolonged hospitalization were analysed using modified Poisson regression.

Results

Among 1143 live born infants, there were 174 hospitalized pneumonia events in 133 children under 2 years. Three children (1.7%) died, 14 (8%) required ICU admission for respiratory support. In modified Poisson regression, age < 2 months, preterm birth, or hypoxia (oxygen saturation <92%) were significantly associated with serious outcomes. Preterm birth, low birth weight, HIV exposure, stunting, or underweight-for-age (UWFA) were associated with prolonged hospitalization. Chest radiography, elevated C reactive protein, white blood cell and neutrophil counts were not useful to predict death or ICU admission in children hospitalized with pneumonia.

Conclusions

In this cohort, death from pneumonia was rare, but clinical features associated with serious outcomes and prolonged hospitalization were identified. These may help with risk stratification, to identify children who may benefit from enhanced monitoring or earlier escalation to respiratory support.

(abstract 277 words)

6.2 Introduction

Global child deaths from pneumonia have decreased substantially over the last 30 years, from 1.7 million in 1990 to 800 000 in 2017.[1] This decline reflects both decreased incidence and severity of pneumonia.[2] However, in low and middle income countries (LMIC), pneumonia remains the largest single cause of under-5 child mortality outside the neonatal period, and severe pneumonia is the most common reason for childhood death and hospitalization.[3]

The World Health Organization (WHO) clinical classification of pneumonia changed in 2013 from 4 categories (no pneumonia, pneumonia, severe pneumonia or very severe pneumonia) to 3 categories (no pneumonia, pneumonia or severe pneumonia).[4] These categories are intended to provide maximum sensitivity to differentiate children with community-acquired pneumonia who can safely be treated as outpatients with oral antibiotics from those who require referral to hospital for assessment and parenteral antibiotics. However, among those referred to hospital, the WHO case definition of "severe pneumonia" does not further identify those at high risk for death or admission to intensive care unit (ICU),[5,6] or those at risk for prolonged hospitalization. Risk stratifying children hospitalized with pneumonia to identify those at highest risk of serious outcomes can inform management, including enhanced monitoring, earlier initiation of supportive therapy or referral to a higher level of care.

A systematic review of hospitalized children identified 56 studies describing factors associated with serious outcomes of pneumonia.[7] Many of these were single-site retrospective cases series, included older children and teenagers (in whom case fatality is much lower), or were conducted before widespread use of conjugate vaccine against pneumococcus (PCV) and *Haemophilus influenzae* type b (HibCV). More recently, the Pneumonia Etiology Research for Child Health (PERCH) study published a pneumonia severity score derived from 1802 HIV-uninfected children under 5 years hospitalized with severe or very severe pneumonia, identifying specific clinical features associated with in-hospital mortality.[8] However, all risk stratification scores are based on clinical signs and radiological features; and are cross-sectional studies, so analysis of the child's early exposure history is limited by recall bias. To our knowledge, there are no pneumonia severity analyses nested within prospective birth cohorts, with detailed information about the early life determinants of disease, including factors around maternal health, birth, breastfeeding and early environmental or other household exposures. Although detailed early life and antenatal exposures may not be amenable for inclusion in pneumonia severity scores, exploring these is important in understanding which exposures place children at risk of serious outcomes.

We previously described incidence, severity and risk factors for pneumonia[9] and respiratory syncytial virus (RSV) pneumonia[10] in children under 2 years of age in the Drakenstein Child Health Study (DCHS), a birth cohort in South Africa. In this paper, we describe factors associated with pneumonia mortality or ICU admission in the first 2 years of life, and test whether the risk factors included in the PERCH severity score were associated with death or ICU admission in this cohort. In addition, we investigate factors associated with prolonged hospitalization for pneumonia in this birth cohort.

6.3 Methods

Study design

The DCHS, a population-based birth cohort established in 2012 in a peri-urban community outside Cape Town, South Africa, has been described in detail.[11,12] The population is of low socio-economic status (SES); unemployment and maternal HIV infection are common. Pregnant women (20-28 weeks' gestation) were recruited and followed through pregnancy and delivery; mother-child pairs were followed through early childhood. For this study, follow-up through the first 2 years of life is included. University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC numbers 401/2009; 651/2013) provided ethical approval. Mothers provided written informed consent at enrolment, with annual renewal.

Study procedures

Trained study staff administered structured interviews and performed home visits antenatally and postnatally. Indoor air particulate matter of diameter 10μm or less (PM_{10}) was measured using an air sampling pump (AirChek 52; SKC, Eighty Four, PA, USA), placed in homes antenatally for 24 hours; the ambient standard was defined as 40 $\mu g/m^3$.[13] Diffusion tubes, placed in homes for 2 weeks, measured toluene concentration (Markes thermal desorption tubes; Llantrisant, UK), as described previously.[14] Maternal smoking was measured by urine cotinine measures collected antenatally and at delivery; the higher measurement was used to assign smoking status, as described previously (non smoker / passive smoker <500ng/ml; active smoker $\geq$ 500 ng/ml).[14]

Pneumonia surveillance was performed using active case finding: mothers were interviewed frequently (every 2 weeks in the first year, every 3 months in the second year) about respiratory symptoms (cough, fast breathing, difficulty breathing). Thus it was possible to retrospectively identify pneumonia events occurring at other facilities or outside the area; where possible, details of these pneumonia events were obtained from clinical records of other facilities.[15] Birth cohort participants presenting to clinics or primary care providers with cough, tachypnoea or difficulty breathing were referred to the research study for assessment in real time. Trained research staff

confirmed tachypnoea and clinical signs. Pneumonia was diagnosed according to revised WHO guidelines when a child had cough or difficulty breathing, with either lower chest wall indrawing (LCWI) or age-appropriate tachypnoea ($\geq$ 50 breaths per minute if 2-12 months, $\geq$40 breaths per minute if $\geq$12 months). Severe pneumonia was diagnosed if children were under 2 months old; or at any age, with a general danger sign (cyanosis, decreased level of consciousness, inability to feed, vomiting everything, seizures).[4] In children with wheezing, pneumonia was not diagnosed if tachypnoea and LCWI resolved following a trial of inhaled bronchodilator (5 puffs of salbutamol via a metered dose inhaler with mask / spacer). Only community-acquired cases were included. Nosocomial pneumonia (new onset respiratory symptoms occurring after hospital admission) and congenital pneumonias (tachypnoea present on the first day of life) were excluded. Pneumonia treatment and decision to admit were at the discretion of treating doctors, not study staff. Indications for hospitalization included hypoxia (oxygen saturation <92% in room air) or inability to take oral medication. Children with severe pneumonia were admitted at Paarl hospital, the single regional hospital; children requiring intensive care unit (ICU) were referred to the affiliated unit 47km away. Children were transferred to ICU for ventilatory support if they remained hypoxic (oxygen saturation <92%) despite oxygen supplementation via nasal prongs or face mask; or for inotropic support if shock was refractory to intravenous fluid therapy.

Age at pneumonia was categorized as under 2 months, 2 to 12 months or over 12 months.[4] Within each age group, duration of hospitalization was calculated; duration >90th centile for age group was considered "prolonged hospitalization". Events occurring 14 days following pneumonia were considered new-onset pneumonia. All children had anthropometry performed; stunting was defined as length-for-age <-2 Z score; and wasting as weight-for-length <-2 Z score on WHO growth charts. Severe tachypnoea or severe tachycardia were defined as respiratory rate or heart rate >99th centile of normal for age.[16]

Blood was drawn for full blood count, differential and C-reactive protein (CRP). CRP was modelled both as continuous and dichotomized at $\geq$40mg/L, as this has previously been explored as a proxy to distinguish bacterial from viral pneumonia.[17] Chest radiograph taken at the time of hospitalization was read by 2 independent doctors trained in the WHO standardized chest radiograph reporting methodology.[18] Radiographs were classified as no consolidation, "other" consolidation, or "primary end point consolidation" (PEPC). A third reader, blinded to readings of the others, resolved discordant results. Sensitivity of CRP$\geq$ 40mg/L to predict PEPC was calculated as "true positives" (children with PEPC and CRP$\geq$40mg/L) divided by all those with "true disease" (all those with PEPC).

Usual care was provided at one of 2 local clinics including the national vaccination schedule: Bacille Calmette Guerin (BCG) at birth; 13 valent pneumococcal conjugate vaccine (PCV) at 6, 14 weeks and 9 months; hexavalent vaccine (diphtheria, tetanus, acellular pertussis, hepatitis B, polio and HibCV at 6, 10, 14 weeks and 18 months); and measles vaccine at 9 and 18 months. HIV-exposed infants were tested with HIV-DNA PCR (Cobas Ampliprep/Cobas Taqman HIV-1, Roche Diagnostics Systems, Inc., Branchburg, NJ) between 6 and 10 weeks, with repeated testing during hospitalization. Testing was repeated with age-appropriate tests at 9 and 18 months and after breastfeeding cessation according to local guidelines.[19] Co-trimoxazole prophylaxis was provided to all HIV-exposed infants from 6 weeks until breastfeeding cessation.

Statistical analysis

Continuous data were compared with median (inter-quartile range, IQR) and Wilcoxon rank-sum test. Factors associated with death/ICU admission or with prolonged hospitalization were analysed with prevalence ratios from modified Poisson regression with robust variance estimation; results of regression are presented as risk ratios (RR) and 95% confidence intervals (CI), as these are equivalent to prevalence ratios.[20,21] Robust standard errors were calculated to account for clusters within individuals. Data were analysed using Stata version 11 (College Station, Texas, USA).

6.4 Results

From March 2012 to March 2015, 1137 pregnant women were enrolled; there were 1143 live births. Risk factors for and incidence of pneumonia in the cohort have been described.[9,10] In the first 2 years of life there were 174 episodes of hospitalized pneumonia. These 174 hospitalizations occurred in 133 children: 82/133 (62%) males; 98/133 (74%) were HIV unexposed, 34/133 (26%) were HIV exposed uninfected (HEU), 1 child was HIV infected. Median age at hospitalization was 4 months (IQR 1.8 – 11.0), table 6.1. Among children hospitalized with pneumonia, maternal smoking (67/160, 43%), indoor air pollution (elevated levels of particulate matter, 63/103, 61%) and stunting (67/173, 39%) were common. Preterm birth (52/174, 30%) and UWFA (50/174, 29%) were less common. Severe tachycardia, severe tachypnoea, lower chest wall indrawing (LCWI) or wheezing were common; 56/171 (33%) were hypoxic. Sixteen children (9%) displayed at least 1 WHO danger sign, of which inability to feed (11 cases, 6%) was the most common. Other danger signs were rarely observed, table 6.1. Pyrexia >38^{0}C axillary temp was more common in children > 12 months than in younger children, table 6.1.

Of the 174 hospitalized pneumonia cases, there were 3 deaths (1.7%); 14 (8%) were admitted to ICU for respiratory support: 8 required intubation and mechanical ventilation and 6 received continuous positive airway pressure (CPAP), table 6.2. One child died in ICU and 2 died prior to ICU transfer.

Fatal pneumonia or ICU admission

Fatal pneumonia or ICU admission were strongly associated with younger age: 2 of the 3 deaths and 8 of the 14 ICU admissions occurred in children under 2 months. In unadjusted modified Poisson regression, age <2 months, preterm birth, and hypoxia were significantly associated with serious outcomes, table 6.3. WHO danger signs of decreased level of consciousness and inability to feed, although rarely observed, were strongly associated with serious outcomes. Low birth weight, maternal smoking, UWFA, stunting, grunting, radiological consolidation (PEPC), and elevated CRP appeared to be associated with increased risk of serious outcomes, but precision for these estimates was limited. Female sex, wasting, duration of illness prior to presentation, and cough not observed were not associated with serious outcomes. Several factors were identified which, although previously associated with pneumonia incidence, were not associated with serious outcomes: male sex, household crowding, HIV exposure, incomplete vaccinations, and inadequate breastfeeding. Children exposed to significant household air pollution, measured by elevated antenatal PM_{10} concentration, had a 3-fold increased risk of a serious outcome, but precision for this estimate was limited by small sample size (RR 3.17, 95% CI 0.38 –26.46).

Duration of hospitalization

Median duration of hospitalization was 3 days (IQR 2-5); children under 2 months had longer duration of hospitalization compared to children over 12 months, 4 days (IQR 2-6) vs 2.5 days (IQR 1-4), p=0.04, table 6.1. HEU children had longer hospitalization (median 4 days, IQR 2-8) compared to HIV unexposed children (median 3 days, IQR 2-4, p=0.004). Prolonged hospitalization was associated with preterm birth, low birth weight, HIV-exposure, never breastfeeding, decreased level of consciousness, UWFA and stunting. Hypoxia, lower chest indrawing and other WHO danger signs were not associated with increased risk of prolonged hospitalization, table 6.3. PEPC on chest radiograph, elevated CRP, total white cell and neutrophil counts were also associated with prolonged hospitalization.

Chest radiography and C-reactive protein

Of 174 pneumonia hospitalizations, 162 (93%) had chest radiographs reported. Overall, 64 (40%) had "primary end point consolidation" (PEPC) and 62 (38%) had "other consolidation". PEPC was equally common in all age categories, table 6.1. CRP result was available for 140/174 (80%) of hospitalized pneumonia events; median CRP was higher in children older than 12 months compared to those aged 2-12 months (p=0.002) or children aged < 2 months (p<0.0001), table 6.1. Children with PEPC tended to have higher CRP levels (median 19 mg/L, IQR 5 – 51) than children with "other

consolidation" (median 10mg/L, IQR 3 – 39) or "no consolidation" (median 4 mg/L, IQR 3 – 18); but only 18/51 (35%) of children with PEPC had CRP>40mg/L. CRP cut-off of 40mg/L did not predict death or ICU admission (sensitivity 42%) or prolonged hospitalization (sensitivity 47%).

6.5 Discussion

In this well-vaccinated birth cohort with negligible HIV infection and reasonable nutritional status, 1.7% of hospitalized pneumonia cases died and 8% required ICU admission. Good access to care and referral may have also contributed to low pneumonia mortality. Young age < 2 months, hypoxia, or preterm birth were strongly associated with death or ICU admission; while low birth weight, stunting, UWFA, HIV exposure, and WHO-defined radiographic consolidation were strongly associated with prolonged hospitalization.

Hypoxia has been considered the most important feature of pneumonia severity.[5,22-24] However, in our cohort, peripheral oxygen saturation <92% was a reason to consider hospitalization, and was very common, occurring in 33% of hospitalized cases. Hypoxia was associated with serious outcomes, but was so common in this cohort that it did not have good discriminatory value among hospitalized children to identify those who require intensive monitoring or additional respiratory support. There are no reliable clinical signs to predict hypoxia in children,[25] which makes pulse oximetry screening and oxygen supply essential for all facilities treating children.[26] .

Preterm delivery confers multiple risks for childhood morbidity, including less transplacental antibody transfer, anaemia, suboptimal breastfeeding, delayed / missing vaccinations, and slower growth.[27,28] Preterm birth is useful as a risk stratification marker where gestational age is accurately known; front-line health care workers can quickly identify at-risk children from patient-held birth records, and prioritise them for urgent assessment and pulse oximetry testing.

The original definition of WHO standardized radiographic consolidation was intended as a proxy marker of bacterial pneumonia for use in vaccine studies,[18] and was strongly associated with mortality.[29] However, there is increasing evidence that much severe pneumonia post PCV and HibCV is viral: 33% of pneumonia hospitalizations in this cohort were associated with RSV,[10] and in the PERCH study, viruses (especially RSV) were predominant causes of hospitalized pneumonia among children with positive chest radiology.[30] In this well-vaccinated cohort, neither radiological consolidation nor elevated CRP were significantly associated with death/ICU admission. Furthermore, although PEPC was associated with higher median CRP, there was no CRP threshold that strongly predicted PEPC. It is increasingly accepted that CRP is a poor marker of bacterial infection.[31,32] This is consistent with the epidemiologic change that has occurred since WHO

radiographic scoring was developed;[33] so PEPC or elevated CRP should no longer be considered a proxy for bacterial infection. Since neither radiological consolidation nor elevated CRP strongly predicted death or ICU admission, and are not widely available in LMIC, they could be excluded from severity scores in favour of more easily-obtainable clinical features.

A recent systematic review of pneumonia risk stratification scores for children in low-resource settings also described hypoxia, LCWI and decreased level of consciousness as strongly predictive for mortality, but that wheeze was protective.[7] A pneumonia risk stratification prediction model developed and validated in a high-income country reported retractions were associated with severe outcomes, but did not report prevalence of wheeze.[6] In our analysis, both wheezing and LCWI were common, but not associated with serious outcomes. This is consistent with evidence that led to WHO reclassification of LCWI as a sign of pneumonia for ambulatory therapy, not a marker of severe pneumonia requiring parenteral therapy;[4] in these young children, where oxygen saturation monitoring was available, LCWI indrawing did not add value in identifying those at risk of severe outcomes.[34]

The PERCH severity score identified infants < 1 year, female sex, decreased level of consciousness, fast breathing without observed cough, grunting, hypoxaemia (peripheral oxygen saturation less than 90%) , duration of illness more than 3 days and severe wasting as risk factors for mortality.[8] The score had a moderate overall predictive accuracy (C statistic 0.76% in a validation data set), but lower predictive accuracy in some age groups (eg age 6-11 months, where mortality was highest) and some sites, including South Africa, where mortality was lowest. The authors recommended that the PERCH score should be validated with other datasets. In our cohort, some of the PERCH predictors were confirmed: young age and hypoxia were strongly associated with serious outcomes. Decreased level of consciousness was infrequently identified, limiting its practical usefulness as a predictor of serious outcomes. Other PERCH predictors performed poorly in our study: female sex, grunting, cough not observed, and longer duration of illness were not associated with serious outcomes; no wasted child died or required ICU admission. Furthermore, the PERCH tool may be impractical for frontline clinicians in LMIC, as it requires careful history from the mother or caregiver, and accurate plotting of weight-for-length, which is often poorly recorded in critically ill children.

A strength of this study is the availability of detailed, longitudinal exposure history prior to pneumonia. Certain environmental factors, measured before the pneumonia event (antenatal maternal smoking, household crowding) were associated with hospitalization for pneumonia,[9] but were not associated with serious outcomes. This suggests that while maternal smoking and household crowding were significant risk factors in the causal pathway for developing pneumonia, they may not be associated with severity; or may have been too common in this cohort to predict serious outcomes

with adequate discrimination. Although elevated household PM_{10} level was not significantly associated with risk of serious outcomes, precision for this estimate may have been limited by sample size. Indoor air pollution plays a critical role in child lung health[14]; this could be investigated as modifiable factor in adequately-powered prospective interventions.

Prolonged hospitalization may be used as a valid measure of pneumonia severity;[35] however, in children with complex co-morbidities, duration of hospitalization may reflect the underlying medical or social problems, and not the severity of the respiratory infection. Preterm birth, HIV exposure, stunting, underweight-for-age, and elevated CRP were significantly associated with prolonged hospitalization. We cannot attribute causality to these associated factors, as reasons for prolonged hospitalization may have been due to the severity of the respiratory infection, but also may have been due to other associated illnesses, nutritional rehabilitation or addressing the social concerns or feeding practices. We previously showed that HEU children have increased incidence of pneumonia in the first 6 months of life;[9] in this analysis we show that they are not at greater risk of serious outcomes, although they are at increased risk of prolonged hospitalization.

Limitations of this study include inadequate power to detect an association, as both death and ICU admission were such rare events; even when they are combined as a composite endpoint of "death or ICU admission", power is limited. Furthermore, use of a composite endpoint requires caution, as some clinical features may reflect the bias of the treating clinician, eg clinicians could be more likely to refer a low birth weight child to ICU, even if the severity of the disease did not require respiratory support. However, this is unlikely as the ICU in the regional referral hospital was 47km away, is a very limited resource, and all children admitted to ICU received invasive or non-invasive ventilation. Some authors consider non-ventilated ICU admissions "moderate" severity, vs death / ventilation ("severe").[5] As we had few events with the composite outcome, we did not analyse "moderate" outcomes separately, but considered all ICU admissions as serious. Prediction models should be derived from one dataset and then applied to a different dataset, or validated with internal bootstrap.[8,36,37] With this small dataset, we were unable to derive a true prediction model; but results compare favourably with predictors from other local and international models. Pneumonia surveillance was strong and consistent throughout the study period; follow up of individuals and overall cohort retention was good, so missed pneumonia hospitalizations or deaths are unlikely. Other missing data, particularly CRP and white cell counts, would not have made substantial impact on outcomes, as most cases with serious outcomes had all blood results available.

In conclusion, we observed low mortality from pneumonia in this cohort. Most of the PERCH severity predictors performed poorly in this cohort. Clinical factors associated with death or ICU admission included age under 2 months, preterm birth or hypoxia. These clinical measures are easily

obtained, do not require radiography, blood tests or interpretation of growth charts, and further underscore the urgent need for more widespread availability of pulse oximeters and oxygen in LMICs. Presence of these risk factors should alert clinicians to identify children who may require additional monitoring or early escalation of care; clinicians should be encouraged to engage in appropriate risk-stratification to identify at-risk children.

6.6 Contributors and acknowledgments

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6.8 Tables

Table 6.1: Characteristics of hospitalized pneumonia episodes

	Age < 2 months (n=47)	Age 2-12 months (n=91)	Age >12-24 months (n=36)
Birth characteristics			
Male, n(%)	31 (65%)	60 (66%)	25 (69%)
Preterm, n(%)	14 (30%)	31 (34%)	7 (19%)
Low birth weight, n(%)	9 (19%)	30 (33%)	10 (28%)
HIV unexposed, n(%) HIV exposed, uninfected, n(%) HIV infected, n(%)	35 (74%) 12 (26%)	61 (67%) 27 (30%) 3 (3%)	29 (81%) 7 (19%)
Exposures			
Maternal education, n(%) Primary only Some secondary Completed secondary	 4 (9%) 26 (55%) 17 (36%)	 11 (12%) 52 (57%) 28 (31%)	 1 (3%) 18 (50%) 17 (47%)
Maternal smoking[1], n(%) (n=156) Non smoker / passive smoker Active smoker	(n=40) 22 (55%) 18 (45%)	(n=82) 41 (50%) 41 (50%)	(n=34) 26 (76%) 8 (24%)
Household crowding, n(%) 6 or more in house	 23 (49%)	 28 (31%)	 12 (33%)
Ever breastfed, n(%)	43 (91%)	80 (88%)	29 (81%)
Indoor air pollution: PM_{10} [2] , n(%) (n=103) Below ambient standard Above ambient standard	(n=21) 10 (48%) 11 (52%)	(n=56) 16 (29%) 40 (71%)	(n=26) 14 (54%) 12 (46%)
Toluene, n(%) (n=105) Below ambient standard Above ambient standard	(n=22) 19 (86%) 3 (14%)	(n=56) 52 (93%) 4 (7%)	(n=27) 23 (85%) 4 (15%)
Routine vaccinations (n=160) All on time, n(%) All given but some late, n(%) Some doses missed, n(%)	(n=39) 21 (54%) 16 (41%) 2 (5%)	(n=87) 44 (51%) 42 (48%) 1 (1%)	(n=34) 20 (59%) 13 (38%) 1 (3%)
WHO danger signs			
Unable to feed	2 (4%)	6 (7%)	3 (8%)
Decreased level of consciousness, n(%)	1 (2%)	1 (1%)	2 (6%)
Vomiting everything	0	3 (3%)	2 (6%)
Convulsions	0	1 (1%)	2 (6%)
Central cyanosis	0	0	1 (3%)
Any WHO danger sign	3 (6%)	9 (10%)	4 (11%)
Clinical features			
Duration of illness prior to presentation, days, median (IQR)	3 (2 – 5)	3 (2 – 4)	3 (1 – 4)
Underweight for age[3], n(%) n=173	11 (23%)	32 (36%)	7 (19%)
Stunted[4], n(%) n=173	17 (36%)	43 (48%)	7 (19%)
Wasted[5], n(%) n=169	5 (11%)	8 (9%)	7 (19%)
Grunting	13 (28%)	18 (20%)	5 (14%)
Head nodding	11 (24%)	6 (7%)	1 (3%)
Cough not observed	22 (49%)	24 (27%)	12 (33%)

Pyrexia >38^{0}C on presentation, n(%)	9 (20%)	44 (50%)	24 (67%)
Pulse rate, median (IQR)	171 (160 – 185)	168 (158 – 182)	159 (146 – 169)
Severe tachycardia[6], n(%)	13 (28%)	46 (50%)	22 (61%)
Respiratory rate, median (IQR)	68 (60 – 72)	60 (56 – 67)	54 (47 – 64)
Severe tachypnoea[7], n(%)	25 (53%)	34 (37%)	23 (64%)
Lower chest indrawing, n(%)	41 (87%)	86 (95%)	23 (64%)
Wheeze, n(%)	22 (47%)	55 (60%)	15 (42%)
Hypoxic (saturation <92%), n(%)	15 (33%)	30 (34%)	11 (31%)
Chest radiograph findings, n(%) (n=162) No consolidation Other consolidation Primary end point consolidation	(n=43) 15 (35%) 13 (30%) 15 (35%)	(n=85) 16 (19%) 33 (39%) 36 (42%)	(n=34) 5 (15%) 16 (47%) 13 (38%)
Laboratory features			
White cell count[8], median (IQR)	10.6 (8.9 – 14.2)	13.4 (10.5 – 16.9)	15.2 (10.6 – 20.7)
Neutrophil count[8], median (IQR)	3.2 (2.4 – 6.3)	5.3 (3.2 – 7.3)	7.3 (5.1 – 16.6)
Neutrophil percentage, median (IQR)	33 (21 – 38)	40 (28 – 52)	56 (38 – 68)
Haemoglobin, g/dL, median (IQR)	11.4 (9.8 – 12.8)	10.1 (9.4 – 11.1)	11 (9.8 – 11.7)
C reactive protein, mg/L, median (IQR)	4 (2 – 20)	8 (3 – 38)	29 (13 – 49)
Outcomes			
Duration of hospitalization median (IQR)	4 (2 – 6)	3 (2 – 5)	2.5 (1 – 4)
Prolonged hospitalization[9]	5 (11%)	10 (11%)	4 (11%)
Died or admitted to ICU[10], n(%)	9 (19%)	7 (8%)	0

1) Based on antenatal urine cotinine: Non smoker / passive smoker <500ng/ml; active smoker ≥ 500 ng/ml
2) Particulate matter <10 micrometer
3) Weight for age <-2 Z score
4) Length for age <-2 Z score
5) Weight for length <-2 Z score
6) Heart rate > 99th centile for age
7) Respiratory rate > 99th centile for age
8) Cell counts: x 10^9/ L
9) Prolonged hospitalization: duration ≥90th centile for age category
10) ICU: Intensive care unit

Table 6.2: Clinical description of children with serious outcomes of pneumonia (death or ICU admission)

Sex	Birth weight, kg	Gestation, months	Age at pneumonia event, months	HIV status	Duration of illness days	Oxygen saturation, percent	WHO danger signs	Chest radiograph WHO category	CRP (mg/L)	Respiratory support	Outcome
Male	3.37	34	0.3	Exposed	(not recorded)	93	Decreased level of consciousness	No consolidation	20	IPPV	Survived
Female	2.69	36	0.8	Unexposed	2	81		Primary end point	117	IPPV	Died
Male	3.31	41	1	Exposed	3	99		Primary end point	4	CPAP	Survived
Male	2.61	39	1	Unexposed	2	93		Primary end point	51	CPAP	Survived
Male	2.46	37	1	Unexposed	1	92		Other consolidation	??	IPPV	Survived
Male	1.30	29	1.5	Unexposed	4	99		No consolidation	4	IPPV	Survived
Male	2.84	36	1.5	Unexposed	1	40		Primary end point	44	IPPV	Survived
Female	3.31	42	1.5	Unexposed	4	73	Unable to feed	Primary end point	7	CPAP	Survived
Male	2.72	40	1.5	Unexposed	2	(not done)		(not done)		(nil)	Died
Male	1.19	27	3	Unexposed	1	94		Primary end point	3	IPPV	Survived
Female	1.06	28	3	Unexposed	3	79		Primary end point		CPAP	Survived
Male	1.06	32	4	Exposed	4	86	Unable to feed	Primary end point	76	CPAP	Survived
Male	1.06	32	5	Exposed	7	85	Decreased level of consciousness Unable to feed	Primary end point	132	IPPV	Survived
Female	3.44	39	6	Unexposed	2	88		Primary end point	11	CPAP	Survived
Male	1.06	32	8	Exposed	2	90		Primary end point		IPPV	Survived
Female	3.19	38	11	Unexposed	2	79		Primary end point	9	(nil)	Died

WHO: World Health Organization
CRP: C reactive protein
IPPV: Intermittent positive pressure ventilation
CPAP: Continuous positive airway pressure

Table 6.3: Factors associated with A) Death or admission to Intensive Care Unit (ICU); and B) Prolonged hospitalization: unadjusted risk ratios from modified Poisson regression

Clinical characteristics	A: Death or ICU admission (n=16)	B: Prolonged hospitalization[1] (n=19)
Birth characteristics	Risk ratio	Risk ratio
Male	1.10 (0.40 – 3.03)	2.66 (0.81 –8.81)
Pre-term	**3.02 (1.18 – 7.69)**	**3.23 (1.37 – 7.57)**
Low birth weight	1.98 (0.78 – 5.05)	**3.51 (1.50 – 8.22)**
HIV unexposed HIV exposed, uninfected HIV infected	1 0.91 (0.31 – 2.68) (unable)	1 **3.74 (1.60 – 8.72)** (unable)
Exposures		
Maternal education, n(%) Primary only Some secondary Completed secondary	 1 1.66 (0.23 – 12.22) 1.29 (0.16 – 10.34)	 1 1.00 (0.25 – 4.07) 0.65 (0.11 – 3.42)
Household crowding: 6 or more in house	0.59 (0.20 – 1.75)	0.46 (0.16 – 1.36)
Maternal smoking: Active smoker[2]	2.32 (0.71 – 7.65)	1.33 (0.45 – 3.95)
Never breastfed	0.46 (0.06 – 3.34)	**3.19 (1.35 – 7.54)**
PM_{10}: Above ambient standard	3.17 (0.38 – 26.46)	1.59 (0.32 – 7.85)
Late or missing vaccinations	1.40 (0.31 – 6.24)	(unable)
WHO danger signs		
Unable to feed	**3.38 (1.12 – 10.15)**	2.74 (0.94 – 8.04)
Decreased level of consciousness	**6.00 (1.99 – 18.10)**	**4.94 (1.68 – 14.58)**
Vomiting everything	(unable)	(unable)
Convulsions	(unable)	3.13 (0.59 – 16.52)
Central cyanosis	(unable)	(unable)
Any WHO danger sign	**3.29 (1.20 – 9.04)**	1.85 (0.60 – 5.70)
Clinical		
Age: over 2 months Under 2 months	1 **3.47 (1.36 – 8.83)**	
Duration of illness prior to presentation, days	0.83 (0.64 – 1.08)	0.78 (0.58 – 1.04)
Underweight for age[3]	2.46 (0.97 – 6.21)	**5.33 (2.14 – 13.27)**
Stunted[4]	1.58 (0.62 – 4.02)	**2.71 (1.12 – 6.56)**
Wasted[5]	0.62 (0.08 – 4.55)	2.29 (0.83 – 6.36)
Grunting	2.50 (0.95 – 6.58)	1.73 (0.71 – 4.25)
Head nodding	1.21 (0.30 – 4.94)	1.00 (0.25 – 4.00)
Cough not observed	1.43 (0.52 – 3.95)	1.53 (0.64 – 3.68)
Pyrexia >38^{0}C on presentation	0.30 (0.09 – 1.04)	0.70 (0.29 – 1.71)
Severe tachycardia[6]	0.69 (0.26 – 1.82)	1.97 (0.81 – 4.77)
Respiratory rate	0.98 (0.94 – 1.02)	0.99 (0.96 – 1.02)
Severe tachypnoea[7]	0.87 (0.34 – 2.24)	0.82 (0.34 – 1.93)
Lower chest indrawing	1.12 (0.27 – 4.64)	1.36 (0.33 – 5.54)
Wheeze	0.89 (0.35 – 2.27)	0.99 (0.42 – 2.32)
Hypoxic (saturation <92%)	**3.08 (1.15 – 8.25)**	1.85 (0.79 – 4.30)
Chest radiograph findings No consolidation	 1	 1

Other infiltrate	0.29 (0.03 – 3.11)	2.32 (0.27 – 20.12)
Primary end point consolidation	3.38 (0.80 – 14.31)	**7.88 (1.07 – 57.81)**
Laboratory features		
C reactive protein		
< 40mg/L	1	**1**
≥40 mg/L	2.41 (0.82 – 7.11)	**3.00 (1.26 – 7.16)**
White cell count	1.02 (0.96 – 1.09)	**1.05 (1.02 – 1.08)**
Neutrophil count	1.00 (0.91 – 1.10)	**1.08 (1.03 – 1.14)**
Neutrophil percentage	1.01 (0.97 – 1.05)	**1.03 (1.01 – 1.06)**
Haemoglobin, g/dL	1.10 (0.76 – 1.59)	0.84 (0.66 – 1.08)

1. Prolonged hospitalization: duration of hospitalization >90th centile, by age category
2. Based on antenatal urine cotinine: Non smoker / passive smoker <500ng/ml; active smoker ≥ 500 ng/m
3. Weight for age <-2 Z score
4. Length for age <-2 Z score
5. Weight for length <-2 score
6. Heart rate >99th centile for age
7. Respiratory rate >99th centile for age

Chapter 7
Summary and recommendations

The aim of this research was to investigate the incidence, severity and determinants, of child pneumonia in a birth cohort of children with high vaccination coverage, in a high-pneumonia burden, low-socio-economic community.

7.1 Context of the Drakenstein Child Health Study

This birth cohort comprising 1137 mothers enrolled antenatally and their 1143 children, is located in a middle-income country in the time of demographic transition. This population, although of low socio-economic status, lives in a peri-urban context; there is universal access to cell phones and 92% of households have electricity. They have excellent access to health care, near-ubiquitous coverage of conjugate vaccines, and excellent prevention of mother-to-child transmission of HIV. Therefore, having optimised several public health interventions, key questions are the magnitude of the residual burden of childhood pneumonia, and the severity and determinants of these pneumonia cases.

7.2 Summary of major findings:

1) **Passive surveillance of pneumonia cases (see Chapter 4)** counted at clinics and hospitals is relatively easy, but significantly undercounts pneumonia cases when compared to the case ascertainment that was performed in the birth cohort. With pneumonia cases that were passively obtained via the community surveillance system, the incidence of pneumonia was estimated at 0.20 (95% CI 0.17 – 0.22) episodes per child-year, whereas when cases identified in the birth cohort were used, the incidence of pneumonia was 0.27 e/cy (95% CI 0.23 – 0.32 e/cy). Incidence as measured by the passive surveillance was significantly lower (incidence rate ratio 0.72, 95% CI 0.58 – 0.89) compared to active surveillance in the birth cohort, and the passive surveillance identified significantly lower proportion of hospitalized cases than the birth cohort (17% vs 39%, $p<0.001$). Accurate estimation of pneumonia incidence is not possible unless the person-time at risk is known. When pneumonia cases are obtained from passive reporting or from routinely-collected health system data, there is uncertainty in the numerator. And when the child population at-risk is estimated from census data that may be several years out of date, there is uncertainty in the denominator. Passively-reported cases and routine health service reports give an indication of burden of disease, access to health care, and health service utilisation in a community, and are valuable to collect and compare temporal trends. But passively reported case counts cannot easily be converted into true population-level incidence rates. The Health System Trust District Health Barometer, pooling sources from National Department of Health information sources, estimated national under 5 pneumonia incidence at that time at 0.04 e/cy.[1] However, it is difficult to correlate our

measured mortality in the first year of life with estimates of under-5 mortality, as the childhood pneumonia mortality decreases sharply after 1 year of age. Furthermore, it was not possible to further link the cases who were misclassified in the surveillance system, so more detailed analysis was not possible. The birth cohort enabled accurate estimation of pneumonia cases and person-time at risk, and exact calculation of true population-based incidence rates.

2) There was a **high incidence of pneumonia (Chapter 5)**. Observed incidence in the birth cohort was high, 0.51 e/cy, in the first year of life during the period studied (2012 to 2017). As expected, pneumonia incidence rate was highest in the first year of life, and decreased subsequently;[2,3] we observed incidence of 0.25 e/cy in the second year of life. The incidence of WHO clinical pneumonia, using the same case definition, was much higher than expected in a community with good coverage of PCV and HibCV, good nutrition, and almost no HIV infection. The Institute for Health Metrics and Evaluation estimated that pneumonia incidence in infants under 1 year in South Africa was between 0.11 and 0.14 e/cy during the same period, while in children under 5 years was between 0.09 and 0.12 e.cy.[4] IHME incidence estimates are modelled on estimates of attributable fractions of pneumonia risk factors, and tend to be lower than other global estimates. For example, the WHO MCEE estimated under-5 pneumonia incidence for South Africa during that period as 0.23 e/cy,[5] nearly double those of the IHME estimate, and yet still much lower than what was measured in the birth cohort. This is important as modelled pneumonia estimates rely on measured data from well-monitored cohort studies. The models and their underlying assumptions need to be adjusted when new data becomes available. The measured pneumonia incidence rates from this birth cohort are highly reliable and as such, will inform the global child health epidemiologists to refine future estimates of incidence of pneumonia cases.

3) Despite high incidence of severe and hospitalized pneumonia, **pneumonia mortality was low, (Chapter 5 and 6)**. In the birth cohort we observed incidence of hospitalized pneumonia of 0.09 e/cy and of WHO severe pneumonia of 0.09 e/cy in children under 2 years, but pneumonia mortality was low: 1.7% of hospitalized cases, and 0.35% of all clinical cases. This is much lower than pneumonia mortality observed in hospitalized children in the PERCH study (6.7%),[6] children under 2 months in Malawi (3.6%),[7] in 12 secondary-level hospitals in Nigeria (6.5%)[8] or in 40 hospitals in Malawi (6.6%).[9] Reasons for lower-than-expected mortality may include good vaccine coverage, including PCV and HibCV; low incidence of HIV infection; good access to clinical care and early antibiotics via community IMCI; and overall good nutritional status, and close follow-up of children in the cohort.

4) **Risk factors for pneumonia did not have fixed effects,** but had different impact at different ages, and variable effect on ambulatory vs hospitalized pneumonia (Chapter 6). In the multivariable regression model, we estimated adjusted incidence rate ratios for both ambulatory and hospitalized pneumonia for 5 risk factors (age <6 months, male sex, LBW, maternal smoking, delayed vaccines) which appeared to have consistent effect across the cohort. However certain risk factors appeared to have different effects at different ages: in this cohort, household crowding was strongly associated with hospitalized pneumonia in first 6 months of life, but there was no significant association with hospitalization in older age groups, and household crowding was not associated with ambulatory pneumonia at any age. Similarly, the **effect of HIV exposure was limited to first 6 months of life,** and was only associated with hospitalized pneumonia. HIV exposed infants had double the incidence of hospitalized pneumonia under 6 months compared to unexposed infants (IRR 1.99, 95% CI 1.11 – 3.54), but this association disappeared in older age groups. In addition, maternal ART regimen was associated with decreased incidence of hospitalized pneumonia in HEU infants: infants born to mothers who used triple ART in pregnancy had half the incidence of hospitalized pneumonia compared to infants whose mothers used short-course nevirapine/zidovudine (IRR 0.49, 95% CI 0.26 – 0.96). This confirms the effectiveness of newer maternal ART regimens on both maternal and also long-term child health.

5) There was **marked variability in annual pneumonia incidence** over the duration of follow-up (Chapter 3, Chapter 5). The incidence of hospitalized pneumonia in infants under 1 increased by 50% in the 2014-15 pneumonia season (0.15 e/cy) compared to 2012-2013 (0.10 e/cy). This year-to-year variability underscores the importance of multi-year long term incidence studies, in the same community and using the same methodologies, to identify and quantify the annual variability.

6) Risk factors for **serious outcomes of pneumonia (death or ICU)** were identified: young age, LBW, hypoxia, (Chapter 6). Some risk factors for pneumonia hospitalization were not associated with serious outcomes: male sex, household crowding, HIV exposure, delayed vaccinations. Precision for the effect of maternal smoking on odds of death or ICU admission was limited by small sample size (OR 1.57, 95% CI 0.83 – 2.95). There were no clinical signs that reliably predicted death or ICU admission; this underscores the critical importance of measuring pulse oximetry in all pneumonia cases to recognise hypoxia and identify children at high risk of death, as well as the need for oxygen at health facilities.

7.3 Strengths and limitations

One of the major strengths of this study was the prospective study of pneumonia incidence and risk factors in a birth cohort. As the person-time at risk was known, it was possible to calculate an accurate population-based incidence rate. As recruitment continued over several years, we could calculate age and season-adjusted incidence rates. Many pneumonia risk factor studies are cross sectional, where information about the exposure and the outcome are obtained at the same time. As this was a population-based birth cohort, it was possible to establish the background prevalence of exposures in the cohort before the pneumonia event occurred; and to measure the relative impact on exposed vs unexposed children. Furthermore, in cross-sectional studies, where risk factors are ascertained at the time of the pneumonia event, it can be difficult to assess certain exposures accurately. Some early-life determinants, like antenatal exposures, and household and environmental factors present in early infancy may not be amenable to sampling or questioning, and even objectively measured parameters like gestational age and birth weight may not be readily available at the time of pneumonia hospitalization. In a prospective cohort, these data were accurately measured in real time, which decreased the risk of recall bias. In addition, as risk factors were evaluated longitudinally, it was possible to look at antenatal and postnatal exposures, and estimate cumulative effects.

Another strength of this research is that we used standard clinical case definitions for pneumonia and severe pneumonia, and standardised definitions for reporting radiological consolidation. This makes our data easily comparable with other clinical and radiological descriptions of pneumonia across time periods and in different geographical areas. Pneumonia surveillance systems, run by well-trained teams of nurses and research assistants, applied these clinical case definitions consistently throughout the study period; we are confident that variability in numbers of reported cases (by season and over different years) represents true variation, as there is unlikely to be periodic or seasonal under- or over-reporting.

A possible limitation of this study is the possibility of over-diagnosis of pneumonia, as mothers were sensitised to the study goals and procedures, and have been more likely to access care than the general population. However, misclassification bias due to over-diagnosis is unlikely, due to strict application of the WHO case definitions, as mentioned above. Another possible limitation relates to the external generalisability of results. As the per study protocol, enrolment was limited to pregnant women over 18 years of age due to the need to obtain informed consent from participants and for them to give consent for their children to be enrolled, who intended to remain in the area, and who accessed ante-natal care in the second trimester. In South Africa, worse perinatal outcomes are experience in teenage pregnancies,[10,11] and unbooked pregnancies.[12,13] Women who are experiencing homelessness are among the most vulnerable to adverse health outcomes.[14-16] However, since these women did not

meet enrolment criteria they were excluded from the DCHS; so our birth cohort has systematically excluded some of the most vulnerable women and children, in whom we may have expected worse outcomes, including higher rates of perinatal HIV transmission, lower rates of vaccinations, and higher mortality. The pneumonia incidence and severity data for this community should be considered the "best case" scenario, as they may not represent the experience of the most deprived children; it is possible that incidence could be higher and severe outcomes may be more common if these very high-risk women had been included.

A further limitation of the study design of a longitudinal birth cohort relates to the cost of establishing and maintaining the cohort, and the cost of the many staff members who were involved in retention efforts, phone calls and home visits over the years. Birth cohorts are very valuable but very expensive to maintain. Furthermore, as enrolment and cases accrue slowly, significant time is elapsed between design and initiation of the study before the results are available. In this case it became necessary to report interim results of pneumonia incidence before the full cohort had been enrolled. Finally, as mentioned above, there was inadequate power to detect an association between many of the explored risk factors and the rare outcomes of death or ICU admission, as these were such rare events in the population-based birth cohort.

7.4 Recommendations:

Policy implications

1) There is ongoing need for **trained staff to identify and treat pneumonia**. Pneumonia still presents a large burden of childhood morbidity, DALY's and potential mortality. Front-line clinical staff need to be able to recognize child pneumonia and initiate therapy.
2) It is imperative that health facilities **provide oximeters and prioritise checking oxygen saturations** of all young children with pneumonia: clinical signs of pneumonia and features of respiratory distress are not sensitive enough to identify hypoxia or predict pneumonia mortality – all children must have oximetry. **Oxygen must be available** at all facilities where children are treated
3) Since delayed vaccination was associated with increased pneumonia incidence, **vaccination programs need to be strengthened**, to provide timely vaccines for all children, and identify children who are at-risk, or have delayed or missed vaccinations. New vaccines for the residual burden of disease are needed: once vaccines for childhood respiratory viruses are available, it is imperative that they are made available for children in LMIC, where the burden of disease is greatest.

4) There is ongoing need for **investment in social determinants of health;** there needs to be legislation and social investment to address **indoor air pollution, household crowding, environmental tobacco smoke, with particular attention to smoking cessation among pregnant women.**
5) Programs that **promote universal lifelong maternal optimal anti-retroviral therapy** must be supported. Attention to maternal ART with good virological suppression and immune restoration will decrease burden of early pneumonia in HEU infants. **Promotion of breastfeeding** may impact growth and other early childhood infectious morbidity, especially diarrhoeal disease; this remains a universal child health priority, although direct impact on pneumonia incidence may be limited.
6) It is important that **facilities and districts continue routine pneumonia reporting;** this will identify annual trends in burden of disease and health care utilisation, and will facilitate resource allocation. Although not directly comparable to true population-based incidence rates, facility-based pneumonia reporting is relatively easy to sustain and provides useful longitudinal health system information.

Future research:

1) Long-term consequences of child pneumonia, and origin of adult chronic pulmonary disease have been described for child pneumonia in the pre-conjugate vaccine era. It is critical that these children who experienced early pneumonia have **careful long-term follow up, clinical assessment and documentation of their lung function.** In the post-vaccine era, where most of child pneumonia is of viral aetiology, the adult sequelae of child pneumonia may be different to that observed several decades ago; there may be relatively more reactive airway disease than previously noted, but lower rates of restrictive lung disease. This birth cohort, with precise documentation of the timing of early childhood exposures, will be useful to clarify the evolving evidence of childhood onset of adult chronic pulmonary disease. This includes the long-term consequences of novel viral infections, eg SARS-CoV2 infections that occurred in birth cohort participants during 2020-2021.
2) The incidence of pneumonia has decreased since introduction of PCV and HibCV; the residual burden is predominantly due to viral agents, but also includes some bacteria, and tuberculosis and fungi. It is important to **quantify the aetiology of the residual burden of childhood pneumonia**, and to identify biomarkers to distinguish bacterial from viral causes, and indicate which children require antibiotic therapy.
3) Since no clinical signs have adequate discriminatory value to reliably identify hypoxia in children with pneumonia, revised clinical care guidelines should include pulse oximetry as part of initial assessment of children with pneumonia**. Implementation research on early**

use of pulse oximetry and early administration of supplemental oxygen must identify if outcomes are improved, with decreased morbidity and mortality compared to children in LMIC who did not have oximetry.

4) Pneumonia incidence rates and risk factors were elucidated for a peri-urban community with good access to health care, low rate of HIV infection, and overall good nutrition status. These **findings should be validated for urban and rural communities,** and in HIV-infected children, and in areas with high rates of malnutrition.

5) In this observational cohort, we demonstrated factors that were associated with pneumonia incidence and severity. However, this study design is not adequate to prove causality; it would be necessary to **design interventional studies that address the root causes,** those upstream determinants of low birth weight, indoor air pollution, maternal smoking. The full contribution of these causes can only be understood when comparing to a counterfactual model in which they are eliminated.

6) There is great need for **novel interventions** (eg diagnostics like point-of-care ultrasound; improved diagnostics for tuberculosis; novel approaches to smoking cessation, household crowding and improved indoor air quality) to **address the considerable residual burden** of childhood pneumonia, with evidence of cost-effectiveness in young children in LMIC.

7.5 Conclusion

Child pneumonia remains a major global public health challenge. Estimation of global incidence of mild or ambulatory pneumonia, burden of severe or hospitalized pneumonia, mortality and pneumonia DALY's requires detailed understanding of population-based incidence, risk-factors and factors associated with severe outcomes. In this research we have presented a unique birth cohort: a low-SES but well-vaccinated population in a middle-income country with very high cohort retention. We have demonstrated higher-than expected incidence of pneumonia, but with very low mortality. These data, carefully measured in this intensively-monitored birth cohort, will have global applicability for estimation of child pneumonia incidence in regions where direct measurement is impossible. We believe that these child pneumonia data can be applied to epidemiology and disease-modelling for child health; they will contribute to long-term morbidity follow-up studies; and they will shape our understanding of the constantly-evolving epidemiology of child pneumonia.

7.6 References

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Appendix A: Ethical approval, UCT Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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04 November 2013

HREC REF: 651/2013

Dr D le Roux
Paediatrics & Child Health
5th floor
Red Cross War Memorial Children's Hospital

Dear Dr le Roux

PROJECT TITLE: AETIOLOGY AND OUTCOME OF AMBULATORY CHILDHOOD PNEUMONIA: A LONGITUDINAL STUDY IN A SETTING WITH HIGH VACCINATION COVERAGE

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

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

Approval is granted for one year until the 30th November 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

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

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix B: Related editorial

Campbell, H; Nair, H. Child pneumonia at a time of epidemiological transition. Lancet Glob Health. 2015 Feb;3(2):e65-6. doi: 10.1016/S2214-109X(14)70308-0.

Comment

Child pneumonia at a time of epidemiological transition

oa OPEN ACCESS

See Articles page e95

Some important changes have occurred in global child health in the past decade. Socioeconomic development, action to address the broad social determinants of health,[1] and the development and implementation of effective child health interventions[2] have resulted in a steady and substantial fall in global child mortality.[3] Mortality due to pneumonia, the leading cause of child death in the past decade, has fallen the most steeply. These changes have also resulted in a changing pattern of pneumonia incidence, cause, and risk-factor effects. Therefore, particularly at this time, reliable information about the epidemiology of pneumonia in low-income and middle-income countries should be collected, disseminated, and used to inform child health policy and priority setting. Since vital statistics and other routine health information are not widely available in the countries and regions with the highest child disease burden, to a large extent researchers are reliant on well designed and implemented population-based research in these settings to provide this essential information.

The excellent birth cohort study reported in *The Lancet Global Health* by Heather Zar and colleagues,[4] done in a periurban area outside Cape Town in South Africa, is a good example of a study that has provided important information about child pneumonia at a time of change. It provides the first incidence estimates of pneumonia and severe pneumonia in a low-to-middle-income country (LMIC) population, with high coverage of both (13 valent) pneumococcal and *Haemophilus influenzae* type b conjugate vaccines, and with roughly a fifth of the cohort being HIV-exposed but uninfected. On a background of falling pneumonia incidence over the past decade,[5] these estimates show that, despite an effective vaccination programme addressing the two major causes of pneumonia death, pneumonia continues to be a major burden on health services in this South African population. Worldwide, it remains a major cause of care-seeking for child illness, attendance at clinics, admission to hospital, and prescription of antibiotics. This study suggests that the modelled annual incidence estimates for South Africa in 2010, using a risk factor model that included HIV, of 0·22 episodes in children aged younger than 5 years, are broadly consistent with estimates reported in Theodoratou and colleagues' study.[6] This finding would equate to 1·12 million new cases in South Africa each year in this age group.

Although pneumococci and *H influenzae* type b are major causes of child death from pneumonia, they account for a small proportion of overall pneumonia episodes[7] and hence, as Zar and colleagues[4] point out, continuing investment in social determinants of pneumonia and scaling up of the coverage of other known effective interventions[2] is needed. This investment should also give priority to cross-sectoral approaches, with action on determinants such as maternal education, with appropriate attention given to address the problems of minority and disadvantaged populations. Investment in innovation to tackle other important causes of the remaining pneumonia burden, such as respiratory syncytial virus and influenza,[8,9] is also needed.

The study also points out some other important aspects of the pneumonia burden. Increasingly, the major pneumonia burden is in the first 2 years of life (rather than the international focus on children aged younger than 5 years).[10] Additionally, severe pneumonia accounting for most pneumonia deaths occurs in the first 6 months of life (in this study 26 of 32 of severe episodes had occurred by age 2 months), which might need increasing attention in programme-priority setting. As part of an epidemiological transition accompanying the trends reported here, wheeze is an increasingly important presentation in children presenting with cough and difficulty breathing (reported in 65% of cases in this study), which merits further research to reduce antibiotic over-treatment and promote correct treatment of wheeze in these children. The male to female incidence ratio of 2:1 is substantially larger than the established (slight) increased pneumonia risk due to so-called biological frailty in boys and points to the need to explore possible gender discrimination in care-seeking. Although the study reports an active surveillance system, this system is in fact an active case ascertainment within an essentially passive surveillance system, which could have led to missed cases (when care was not sought) and differential care-seeking by gender. Alarming levels of differential hospital admissions of children with pneumonia by gender have been reported in some LMICs.[11] If the full effect of effective interventions against childhood pneumonia is to be

Comment

realised, then gender discrimination in some countries needs to be recognised as a major source of inequity in child health. Reporting of child health data by sex, as in this study, needs to be seen as an essential element of good practice in the reporting of child health data so that attention can be drawn to sex discrimination, where it exists.

The study reports the occurrence of several episodes of pneumonia in a high proportion of children (with about 40 of 141 episodes representing repeat episodes; 22 children had two episodes and nine children had three episodes out of 141 pneumonia episodes). More insight could have gained if more information was known about these children. Did they have a greater prevalence of known risk factors, such as malnutrition, low birthweight, lack of exclusive breastfeeding, or HIV exposure, than expected in this population? Targeted monitoring of these children over the subsequent few months might be justifiable. Whether all or most episodes were acute in nature would be interesting to know, as well as whether a substantial proportion were due to chronic infections (with some of the apparent repeated episodes truly representing episodes with a more chronic course).

The highly seasonal pattern is consistent with a largely viral cause and has implications for health service and logistical planning to ensure availability of essential health commodities throughout the year. The separate identification of fast breathing in the first day of life as being due to causes other than pneumonia, such as congenital causes, is important, as well as recognition that interventions other than simply antibiotics could be used.

High-quality birth cohort studies are expensive and challenging to do and need a well supported research group with a high level of technical capability and expertise. This study is a good example of such a study yielding reliable data that can inform child heath planning, raise important child health policy issues that merit further investigation, and identify important issues for future research.

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We declare no competing interests.

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Appendix C: Authorisation letters from co-authors

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12 January 2021

Professor and Chairman: Faculty Doctoral and Masters Committee
Faculty of Health Sciences
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Dear Prof Lambert,

Permission Letter as Co-author with Dr Dave le Roux to include Publications in PhD Submission

I was a co-author with Dr le Roux on the following publications:

1) **Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study.** le Roux, DM, Myer, L, Nicol, MP, and Zar, HJ; Lancet Glob Health. 3(2); 95–103. doi: 10.1016/S2214-109X(14)70360-2.

2) **Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors.** le Roux, DM, Myer, L, Nicol, MP, Vanker, A, Stadler JAM, von Delft, E and Zar, HJ. Clinical Infectious Diseases Oct 15, 2019. doi: 10.1093/cid/ciz017.

3) **Factors associated with severity of pneumonia among children in a birth cohort in South Africa.** le Roux, DM, Nicol, MP, Vanker, Nduru, PM and Zar, HJ. (Manuscript submitted to PLOS One and is undergoing peer review)

I concur that Dr le Roux (student number LRXDAV004) was the primary author of the manuscript, and I give permission for these publications to be included in his PhD thesis.

Kind regards,

Landon Myer

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Professor and Chairman: Faculty Doctoral and Masters Committee
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Dear Prof Lambert,

Permission letter as co-author with Dr Dave le Roux to include publications in PhD submission

I was a co-author with Dr le Roux on the following publications:

1) **Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors.** le Roux, DM, Myer, L, Nicol, MP, Vanker, A, Stadler JAM, von Delft, E and Zar, HJ. Clinical Infectious Diseases Oct 15, 2019. doi: 10.1093/cid/ciz017.

2) **Factors associated with severity of pneumonia among children in a birth cohort in South Africa.** le Roux, DM, Nicol, MP, Vanker, Nduru, PM and Zar, HJ. (Manuscript submitted to PLOS One and is undergoing peer review)

I concur that Dr le Roux (student number LRXDAV004) was the primary author of the manuscript, and I give permission for these publications to be included in his PhD thesis.

Kind regards,

A/Prof A Vanker
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Dear Prof Lambert,

Permission letter as co-author with Dr Dave le Roux to include publication in PhD submission

I was a co-author with Dr le Roux on the following publication:

Factors associated with severity of pneumonia among children in a birth cohort in South Africa. le Roux, DM, Nicol, MP, Vanker, Nduru, PM and Zar, HJ. (Manuscript submitted to PLOS One and is undergoing peer review)

I concur that Dr le Roux was the primary author of the manuscript, and I give permission for this publication to be included in his PhD thesis.

Kind regards,

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Professor and Chairman: Faculty Doctoral and Masters Committee
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Dear Prof Lambert,

Permission letter as co-author with Dr Dave le Roux to include publication in PhD submission

I was a co-author with Dr le Roux on the following publication:

Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors. le Roux, DM, Myer, L, Nicol, MP, Vanker, A, Stadler JAM, von Delft, E and Zar, HJ. Clinical Infectious Diseases Oct 15, 2019. doi: 10.1093/cid/ciz017.

I concur that Dr le Roux (student number LRXDAV004) was the primary author of the manuscript, and I give permission for this publication to be included in his PhD thesis.

Kind regards,

.....

Dr JAM Stadler
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2 January 2021

Professor and Chairman: Faculty Doctoral and Masters Committee
Faculty of Health Sciences
University of Cape Town

Dear Prof Lambert,

Permission letter as co-author with Dr Dave le Roux to include publication in PhD submission

I was a co-author with Dr le Roux on the following publication:

Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors. le Roux, DM, Myer, L, Nicol, MP, Vanker, A, Stadler JAM, von Delft, E and Zar, HJ. Clinical Infectious Diseases Oct 15, 2019. doi: 10.1093/cid/ciz017.

I concur that Dr le Roux (student number LRXDAV004) was the primary author of the manuscript, and I give permission for this publication to be included in his PhD thesis.

Kind regards,

Dr E Von Delft
Paarl Hospital and Provincial Government of the Western Cape

Appendix D: Different methodologies of estimating global childhood pneumonia incidence and mortality

Historical context: 2 different methods of childhood pneumonia incidence estimation

Estimation of global incidence of child pneumonia is challenging; areas with highest child pneumonia burden and mortality tend to have poor quality data on pneumonia cases, hospitalizations and deaths.[1] Thus pneumonia cases cannot simply be counted: pneumonia events are modelled based on what limited data are available at national or regional level. The first comprehensive estimate of the incidence of pneumonia in children under 5 years in developing countries was calculated by the Child Health Epidemiology Reference Group (CHERG) using 28 community-based longitudinal studies conducted in 18 developing countries between 1967 and 1991, before widespread introduction of PCV and Hib.[2] It was estimated that 150.7 million episodes of pneumonia occurred in children under-5 years in the year 2000, at an annual incidence of 0.28 episodes per child year.[2] The CHERG group expanded on the 2000 pneumonia incidence analysis in 2008 with increased detail about pneumonia aetiology and mortality.[3] In 2013, they published revised pneumonia incidence and mortality estimates for 2010; they used 35 cohort studies between 1990 and 2010 to estimate global under-5 pneumonia deaths at 1.396 million.[4] Also in 2013, a different research body, the Institute for Health Metrics and Evaluation (IHME), based at the University of Washington in Seattle, published the Global Burden of Disease (GBD) 2010 report. The IHME/GBD researchers used different data sources to the CHERG group, and performed a very different analysis; they estimated that there were 0.847 million under-5 pneumonia deaths in 2010, which was about half the estimate of the CHERG.[4]

Current estimates of child pneumonia

The CHERG group was re-incorporated as the Maternal and Child Epidemiology Estimation (MCEE) group within the WHO. Subsequent global under-5 mortality estimates have converged, with IHME/GBD estimating 5.6 million under-5 deaths in 2016, vs 5.4 million for MCEE.[5] However the estimates for pneumonia incidence and deaths have remained different: the MCEE group estimated 138 million under-5 pneumonia cases in 2015, with an incidence of 0.23 e/cy; that there were 16.4 million under-5 pneumonia hospitalisations, and 900 000 pneumonia deaths.[6] The GBD/IHME group estimated that in 2016 there were 68 million pneumonia episodes in children under-5 years, equivalent to 0.11 e/cy; that there were 5.1 million under-5 pneumonia hospitalization and 652 000 pneumonia deaths.[7]

Methodological differences between the research groups may explain apparent discrepant results. For example, the MCEE model calculates country-specific incidence rates by applying measured incidence rates in the region and national-level prevalence of 7 risk factors: malnutrition (weight for age Z score <-2SD), low birth weight, non-exclusive breastfeeding, indoor air pollution, household crowding, incomplete immunisation and HIV infection. They listed 46 community-based cohort studies that measured pneumonia incidence between 1980 and 2016 that were used for their regional pneumonia incidence estimates. These cohorts were from sub-Saharan African (8), Latin American (5), Eastern Mediterranean (2), South East Asia (14), and Western Pacific (17). Most cohorts measured pneumonia incidence for all children under-5 years; 4 cohorts each reported pneumonia incidence under 3 and under 2 years, and 1 cohort reported incidence in the first year of life. What is striking is that 33 cohorts had completed data collection before 2000; only 1 cohort was actively recruiting participants after the implementation of both PCV and Hib. There was only 1 birth cohort which had detailed information on antenatal exposures (maternal health, smoking, household air pollution), as well as perinatal history and longitudinal follow up through childhood.[6]

The IHME/GBD model on the other hand calculates attributable fractions of 12 different risk factors (stunting, underweight, wasting, handwashing, breastfeeding, second-hand smoking, zinc deficiency, household air pollution, ambient particulate matter pollution, antibiotic treatment, Hib vaccine and pneumococcal vaccine).[7] However, how the modelling is performed to generate the estimates has not been explicitly explained.[1]

Despite using different methodologies[8 9] and some different data inputs, both IHME and MCEE groups agree on broad trends in global pneumonia epidemiology: decreasing incidence of pneumonia, and decreasing numbers of all-cause and pneumonia-specific child deaths. The accompanying editorial of the MCEE report praised the consistency and transparency of the group's methods over 15 years,[10] while the editorial on the IHME/GBD report commented on the "contentious" methodological challenges in this field.[1] Thus each group and methodology is internally consistent, but the two groups estimates, while showing broadly similar trends, do not make for easy comparisons of a single point estimate or a single region at different time points.

What is especially striking, when looking at current pneumonia incidence estimates, is how old and outdated are some of the sources that are used in the models. The latest MCEE estimate incorporated 46 community-based cohort studies that measured pneumonia incidence between 1980 and 2016.[6] But 33 cohorts had completed data collection before 2000; only 1 cohort was actively recruiting participants after the implementation of both PCV and Hib. There was only 1 birth cohort which had detailed information on antenatal exposures (maternal health, smoking, household air pollution), as well as perinatal history and longitudinal follow up through childhood.[6] As the only way to

estimate current pneumonia incidence and mortality is by modelling prevalence of risk factors, it is essential to generate contemporary measured prevalence of pneumonia risk factors and subsequent incidence and severity of pneumonia, including ambulatory events, hospitalisations and deaths.

Current estimates of child pneumonia: ambulatory events

The 2 research groups' estimates of child pneumonia mortality (900 000 vs 652 000) are similar, and are within the uncertainty bounds of one another. However, the estimates of annual pneumonia hospitalisations (16.4 million vs 5.1 million) are more divergent; and the difference in the number of ambulatory pneumonia events is striking: 161 million vs 63 million. This is concerning as neither of the groups actually measure ambulatory pneumonia: the case numbers and incidence estimates are derived from the prevalence of risk factors and attributable fractions in different models, and much of the data that informs the models is several decades old. The underlying assumptions regarding the number of presumed ambulatory events for every documented pneumonia hospitalization or death are based on data collected when many risk factors were more prevalent; many children had simultaneous high-dose exposure to multiple risk factors, in the absence of effective pneumonia case management and conjugate vaccines. The epidemiology of childhood pneumonia has changed so much in the last 30 years, that estimates of the number of uncounted ambulatory episodes per observed death are subject to great uncertainty. As ambulatory pneumonia is less well-studied than hospitalised pneumonia, the knowledge gaps in this area are substantial.

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