Characteristics of and factors associated with infectious disease hospital admissions in children by HIV-exposure status in an era of high coverage of prevention of vertical HIV transmission in the Western Cape Province of South Africa

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ABSTRACT

In South Africa, an estimated 22% of children under age 15 years are exposed to HIV and uninfected (HEU). Since the implementation of lifelong antiretroviral therapy (ART) for all pregnant women living with HIV in 2013 (Option B+) and all individuals living with HIV in 2016 (Universal ART), the proportion of children conceived while their mothers are on ART has increased. Previous research suggests that improved maternal health, due to ART, reduces the excess risk of poor health outcomes, including infectious disease hospital admissions, among children HEU vs. children unexposed to HIV and uninfected (HUU). Conversely, ART initiation before conception may result in higher risk of adverse birth outcomes (e.g. preterm delivery, which may drive increased risk of subsequent mortality and morbidity) compared to ART initiation after conception.

Using routine healthcare data from the Western Cape (WC) Provincial Health Data Centre, this research aims to characterise the temporal changes in HIV-related characteristics of hospitalised children and their mothers and investigate whether child infectious morbidity and healthcare utilisation vary by HIV exposure and maternal ART use status, during the Option B+ and Universal ART eras. The sample size of children included in this research ranges across chapters from N=52,811 (children with infectious disease admissions 2008 – 2021) to N=549,782 (all children born 2008 – 2018).

This thesis uses standardised definitions to systematically classify HIV exposure status of each child. It then describes changes in HIV-related characteristics of children with infectious disease hospitalisations across the WC from 2008 to 2021, showing a decrease in the proportion of admitted children living with HIV and an increase in the proportion of HIV-exposed children exposed to ART from conception, which highlights the success of HIV vertical transmission programmes. A comparison of infection-related hospitalisation rates demonstrates that children HEU vs. HUU experience higher rates of hospitalisation, irrespective of maternal ART history, during the first year of life. Finally, complete routine child healthcare clinic visit attendance among children HEU is seen to be associated with maternal ART start before pregnancy with no gaps in ART care, compared to maternal ART start later in pregnancy with or without gaps in ART.

This thesis concludes that better coverage and implementation of existing interventions, as well as the introduction of more multi-faceted interventions, is required to ensure that both children HEU and HUU survive and thrive. Furthermore, this thesis demonstrates that electronic healthcare platforms play an important role in identifying children that require additional support and targeted interventions.

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AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award (other than one authorised as part of a dual or joint award approved in advance by the University). Except where indicated by specific reference in the text, the work is my own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE:....08 June 2024.....

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s):

1. de Beer ST, Slogrove AL, Eley B, Ingle SM, Jones HE, Phelanyane F, Anderson K, Kalk E, Boulle A, Davies MA. Change in HIV-related characteristics of children hospitalised with infectious diseases in Western Cape, South Africa, 2008-2021: a time trend analysis. J Int AIDS Soc. 2023 Oct;26(Suppl 4):e26151.
2. de Beer ST, Davies MA, Phelanyane F, Jones HE, Ingle SM, Eley B, Anderson K, Heekes A, Kalk E, Mendelsohn A, Boulle A, Slogrove AL. The retrospective implementation of standardised *in utero* HIV exposure definitions using routinely collected public sector data across the Western Cape Province, South Africa. Submitted to the Pediatric Infectious Disease Journal (PIDJ) in July 2023. *The manuscript has undergone review and I have submitted a revised manuscript as of March 2024.*

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LIST OF ABBREVIATIONS

ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral
CI	Confidence interval
CWH	Children with HIV
DECIPHER	Data Evaluation and Collaborative Initiation for Paediatric HIV Education and Research (CIPHER) Preparation for an HIV Exposed Uninfected Child CohoRt)
FDC	Fixed dose combination
HR	Hazard ratio
HEU	Children with HIV exposure who are uninfected
HUU	Children HIV unexposed and uninfected
ICU	Intensive care unit
IYCF	Infant and Young Child Feeding
IRR	Incidence rate ratio
LBW	Low birth weight
LMICs	Low and middle income countries
LRTI	Lower respiratory tract infection
MOU	Midwife Obstetric Unit
NVP	Nevirapine
OPD	Outpatient department
OR	Odds Ratio
PCR	Polymerase Chain reaction
PR	Prevalence ratio
PMI	Patient Mater Index
PrEP	Pre-exposure prophylaxis
RCT	Randomised control trial
RiR	Risk Ratio

RSV	Respiratory syncytial virus
SA	South Africa
sdNVP	Single-dose nevirapine
SES	Socioeconomic status
SGA	Small for gestational age
SHINE	Sanitation, Hygiene, Infant, Nutrition, Efficacy
SMARTT	Surveillance Monitoring for ART Toxicities
SSA	Sub-Saharan African
TBM	Tuberculous Meningitis
UNAIDS	Joint United Nations Programme on HIV/AIDS
URTI	Upper respiratory tract infection
VLBW	Very low birth weight
VTP	Vertical transmission prevention
WC	Western Cape
WCPHDC	Western Cape Provincial Health Data Centre
WHO	World Health Organisation

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PUBLICATIONS ARISING FROM THIS WORK

Below is a list of publications that have arisen from research undertaken throughout this PhD along with the contributions section from each publication.

The following publication is based on Chapter 3

de Beer ST, Davies MA, Phelanyane F, Jones HE, Ingle SM, Eley B, Anderson K, Heekes A, Kalk E, Mendelsohn A, Boulle A, Slogrove AL. The retrospective implementation of standardised *in utero* HIV exposure definitions using routinely collected public sector data across the Western Cape Province, South Africa. Submitted to the Pediatric Infectious Disease Journal (PIDJ) in July 2023. *The manuscript has undergone review and I have submitted a revised manuscript as of March 2024.*

Author contributions: SdB, MAD, ALS, BE, SMI and HEJ conceptualised the analysis. SdB managed the data with assistance from FP and insight from MAD, ALS, KA, AH, EK and AM. SdB conducted the data analysis and drafted the manuscript with subject matter expertise and/or scientific oversight from MAD, ALS, BE, SMI, HEJ and KA. AB provided data engineering oversight within the WCPHDC. SdB incorporated all relevant co-author comments and finalised and submitted the manuscript. All authors reviewed and approved the final manuscript.

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Cape Provincial Health Data Centre. SdB incorporated all relevant comments from co-authors and finalised and submitted the manuscript. All authors reviewed and approved the final manuscript.

LANGUAGE NOTE

While pregnant and breastfeeding people include those with gender identities other than being women, the majority of pregnant and breastfeeding people do identify as women. To adequately convey the distribution of pregnancy and breastfeeding episodes being mainly among women and in the interests of readability and conciseness, I will be referring to pregnant and breastfeeding people using the term “pregnant and/or breastfeeding women”, as appropriate, throughout this thesis. The terminology should however be read to include people who are pregnant or breastfeeding and do not identify as women. The term “pregnancy” or “pregnant” is also considered to include a possible breastfeeding period even if the words “and/or breastfeeding” are not explicitly stated.

Throughout this thesis I will refer to children exposed to HIV and not known to be living with HIV as children with HIV-exposure who are uninfected (HEU). The term “HIV-exposed” will refer to both children living with HIV and those living without HIV who are born to women living with HIV.

Throughout the thesis I refer to routine child healthcare clinic visits for growth monitoring and immunisations as “well-child visits” as this is how they are known in South Africa.

CHAPTER 1. INTRODUCTION AND LITERATURE REVIEW

1.1. Introduction

Globally there were an estimated 1.2 million (uncertainty range: 940,000 – 1.5 million) pregnant women and people with other gender identities (hereafter referred to as "pregnant women")[a] living with HIV in 2022 (1). With effective HIV vertical transmission prevention (VTP) strategies in place, substantial progress has been made in reducing vertical transmission rates in countries with a high prevalence of pregnant women living with HIV (2). As a result, there is an ever-growing population of children who are HIV-negative and who were HIV-exposed *in utero*, at birth and potentially during breastfeeding, i.e. children with HIV exposure who are uninfected (HEU). Modelled estimates suggest that, in 2018, five sub-Saharan African (SSA) countries, namely: Nigeria, Mozambique, South Africa (SA), Tanzania and Uganda, accounted for 50% of the global population of 14.8 million (uncertainty range: 11.1 million – 18.3 million) children who were HEU at the time (3). The largest proportion of the global population of children who were HEU in 2018 (estimated 24% of 14.8 million) resided in SA, where 22% of all children aged under 15 were estimated to be HEU. Since then, the global population of children HEU has increased to 16.0 million (uncertainty range: 12.7 million – 18.4 million) of which 4.1 million (uncertainty range: 2.7 million – 5.2 million) (26%) reside in SA (4).

Infectious morbidity/mortality can be defined as illness/death caused by pathogenic microorganisms, e.g. viruses or bacteria, which can be transferred, directly or indirectly, between people (5). Infectious diseases account for a large proportion of hospital admissions in children and are a leading cause of paediatric morbidity and mortality worldwide (6). Common infectious diseases include lower respiratory tract infections (LRTIs), diarrhoeal diseases, meningitis, malaria and neonatal sepsis. Although study results have been

[a] See language note prior to Chapter 1

inconsistent (mainly due to heterogeneity between studies), evidence pre-dating lifelong access to antiretroviral therapy (ART) for pregnant and breastfeeding women living with HIV, regardless of CD4 count and clinical disease severity (also known as "Option B+"), suggests that the risk of infectious morbidity and mortality among children HEU exceeds that of children HIV unexposed and uninfected (HUU) (7–12). This association between HIV exposure status and poor health outcomes among children who are HEU is believed to be driven by a combination of behavioural, biological, immunological, health system, maternal and social factors (13). Factors such as being born preterm (<37 weeks gestation) / low birth weight (LBW) (<2500g) / small for gestational age (SGA) (birth weight <10th percentile for gestational age), poor nutrition, exposure to infectious pathogens, poor maternal health, and suboptimal breastfeeding are thought to occur more frequently in children who are HEU compared to HUU (9). As HIV exposure may lead to an increased risk of these factors, which themselves increase predisposition to infectious diseases, it is hypothesised that they may mediate the pathway between HIV exposure and infectious disease outcomes among children who are HEU (14). Furthermore, there are additional factors that are mostly unique to children who are HEU e.g. an HIV-affected *in utero* environment, antiretroviral drug exposure, and compromised maternal immunity (9,15,16).

Breastfeeding and maternal ART use have been highlighted as important determinants of infectious disease risk in infants (17). Breastfeeding decreases child morbidity and mortality (18,19) and ART for mothers living with HIV enhances maternal health, which will positively impact on the factors driving poor child health outcomes (17). The World Health Organisation (WHO) guidelines were updated a) in 2010 to recommend exclusive breastfeeding for 6 months and continued nonexclusive breastfeeding (with appropriate complementary foods) for ≥12 months for mothers living with HIV in settings with antiretroviral interventions in place (20), b) in 2013 to recommend Option B+ (21), and c) at the end of 2015, recommending ART initiation for all individuals living with HIV (known as Universal ART) (22), meaning that more mothers could initiate ART before pregnancy. It is hypothesised that the shift toward breastfeeding, ART for all pregnant women living with HIV and ART start before onset of severe illness in all women could reduce the risk of infectious morbidity and mortality among children who are HEU (11,18,19).

By 2020, very few SSA studies had investigated the infectious morbidity and mortality in children who are HEU compared to HUU in the era of Option B+/Universal ART and longer duration breastfeeding. A 2020 study by le Roux *et al.* indicated that, despite breastfeeding and maternal ART that was initiated during pregnancy, children who were HEU compared to HUU had increased prevalence of non-hospitalisation infectious morbidity (pneumonia and diarrhoea) in the first 6 months of life (17). An increase in the risk for infection-related hospitalisation was also observed for children who were HEU relative to HUU between 8 days and 3 months of life. Among children who were HEU, rates of hospitalisation were highest for those whose mothers initiated ART later during pregnancy and had advanced HIV. The observed association was, however, mitigated among children who were HEU, who were vaccinated timeously and whose mothers exclusively breastfed and initiated ART earlier in pregnancy (17). Additional studies have since shown supporting evidence that children HEU compared to HUU remain at increased risk for infection-related hospitalisation during the Option B+ era (23) and Universal ART era (24). Each of the three above mentioned studies enrolled women from one or two primary care facilities, with the largest sample size being 1136 children (247 HEU; 889 HUU). The question remains as to whether these results are generalisable on a larger scale.

In this thesis, I used routine healthcare data to explore infectious disease morbidity in children HEU compared to HUU at a provincial level and within the real-world context of longer duration breastfeeding and the Option B+ and Universal ART eras, in the Western Cape (WC) Province, SA. I assessed how the HIV-related characteristics of children hospitalised with infectious diseases have changed over time; the hospitalisation rates in children HEU vs. HUU; and whether paediatric engagement in well-child visits differs by maternal engagement in HIV VTP services. The specific aims and objectives are provided in Section 1.3. First, I present a review of the literature on all-cause morbidity and mortality, as well as infectious disease morbidity, in children HEU compared to HUU, within the context of changing maternal ART and breastfeeding guidelines.

1.2. Literature review

1.2.1. The history of maternal antiretrovirals, neonatal postnatal prophylaxis and breastfeeding

The last two decades have seen several changes in global and SA antiretroviral and breastfeeding policies, aiming not only to optimise maternal and child health, but also pursue elimination of vertical HIV transmission. Here, I provide a brief summary of the major policy changes that have occurred over time, globally (according to WHO guidelines) and in SA.

Maternal antiretroviral prophylaxis and treatment:

In 2000, the WHO released the first recommendations for using antiretrovirals for the prevention of vertical HIV transmission (Figure 1.1), with progressively more effective regimens being recommended over time (25). The 2010 guidelines recommended lifelong ART for eligible pregnant women living with HIV and short-term prophylaxis, referred to as Option A or Option B, for pregnant women living with HIV not eligible for ART (26). Option A comprised zidovudine (AZT) during the antepartum period, single-dose nevirapine (sdNVP) and the first dose of AZT/lamivudine (3TC) at the onset of labour, and AZT/3TC for seven days postpartum while Option B consisted of triple antiretrovirals which were to be discontinued one week after breastfeeding cessation. Whereas ART aimed to both reduce vertical HIV transmission and improve maternal, and child, health and quality of life, antiretroviral prophylaxis solely aimed to prevent vertical transmission of HIV. ART eligibility criteria included all pregnant women living with HIV with CD4 count <350 cells/μL, regardless of WHO clinical staging, or alternatively, clinical stage 3 or 4, regardless of CD4 count (26).

In 2011, the Global Plan, aiming to keep mothers alive and virtually eliminate the vertical transmission of HIV by 2015, was launched. It prioritised the 22 countries with the highest prevalence of pregnant women living with HIV (together accounting for around 90% of the global population of pregnant women living with HIV), of which 21 countries were located in SSA and one in Asia (India) (27). Following this, 2013 saw a paradigm shift as WHO guidelines were updated to recommend access to ART for all pregnant women living with HIV, irrespective of CD4 count or WHO clinical stage (Option B+) (21). Of the Global Plan countries,

all except Nigeria had accepted Option B+ by 2015 (2). The advantages of Option B+ include: increased access to ART for pregnant women living with HIV, simplification and improved efficiency of the prevention of vertical HIV transmission programme, maintaining maternal health and improved maternal health prior to future pregnancies, the protection against vertical HIV transmission from conception in future pregnancies, and eliminating the starting and stopping of antiretroviral drug use (28). At the end of 2015, WHO updated their guidelines to include access to ART for all people living with HIV, regardless of disease severity (Universal ART) (22).

In SA, the 2010 HIV VTP guidelines were in line with the WHO 2010 guidelines in terms of criteria for initiating lifelong ART or antiretroviral prophylaxis (29). The fixed dose combination pill (FDC) (tenofovir disoproxil fumarate (TDF), emtricitabine (FTC)/3TC & efavirenz (EFV)) was introduced in SA in 2013 with the hope of improving ART adherence (30). In the WC province of SA, the provincial prevention of vertical HIV transmission guidelines were amended to recommend Option B+ in 2013 (31). The shift to Option B+ across all provinces in SA occurred in 2015, meaning that there was a period of discrepancy in the implementation of Option B+ in the WC vs. the rest of SA. Universal ART was implemented in SA in 2016 (32).

The maternal ARVs recommended for use during this study period are described in Table 1.1 (31,33,34).

Table 1.1: Maternal HIV antiretroviral regimens recommended by National and/or Western Cape guidelines during the study period[+](31,33,34)

Treatment	**Regimen (2008 – 2013)**	**Regimen (2013 – 2016)**	**Regimen (2016 – 2018)**
ARV prophylaxis (woman with CD4 cell count >350 cells/ µL)	AZT from 14 weeks gestation sdNVP + AZT during labour single dose TDF +FTC after delivery	*All pregnant women were to receive lifelong ART	*All people living with HIV were to receive lifelong ART
Lifelong ART	TDF + 3TC/FTC + NVP (first line)	TDF + FTC/3TC + EFV (first line)	TDF + FTC/3TC + EFV (first line)

AZT/TDF + 3TC/FTC +LPV/r (second line)	AZT + TDF + 3TC/FTC +LPV/r (second line)	AZT + TDF + 3TC/FTC +LPV/r (second line)

[†] Recommendations may differ based on contraindications

Abbreviations – ARV: antiretroviral; ART: antiretroviral therapy; AZT: Zidovudine; EFV: Efavirenz; FTC: Emtricitabine; 3TC: Lamivudine; NVP: Nevirapine; LPV/r: Lopinavir/ritonavir; sdNVP: single dose Nevirapine

Neonatal postnatal prophylaxis:

Infant postnatal prophylaxis (antiretroviral and non-antiretroviral) provincial guidelines for children HEU during this research period are described in Table 1.2 (31,35):

Table 1.2: Western Cape guidelines for infant postnatal prophylaxis for children HEU, prior to and post 2015 (31,35)

Medication	**Guidelines prior to 2015**	**Guidelines from 2015 onwards**
Nevirapine	▪ Daily for four weeks postnatally for infants at low risk of acquiring HIV / exclusively formula fed infants ▪ Daily for 12 weeks postnatally for breastfed infants at high risk of HIV transmission	▪ Daily for six weeks postnatally for infants at low risk of acquiring HIV / exclusively formula fed infants ▪ Daily for 12 weeks postnatally for breastfed infants at high risk of HIV transmission
Zidovudine	None	Twice daily for infants at high risk of HIV transmission
Cotrimoxazole Prophylactic Treatment	From age six weeks until six weeks post breastfeeding cessation for all infants HEU	From age six weeks until six weeks post breastfeeding cessation for infants HEU at high risk of vertical HIV transmission during breastfeeding

Abbreviations – HEU: HIV exposed uninfected

The guidelines designated infants as at high or low risk of HIV transmission based on the timing of their mother's HIV diagnosis, the duration that their mothers were on ART for prior to child birth, and maternal viral load as follows (Table 1.3):

Table 1.3: Guideline classification of vertical HIV transmission risk for infants/children HEU (31,35)

Risk classification for infants HEU	**Criteria**
Low risk of HIV transmission at birth	▪ Mother on ART and has HIV viral load <1000 copies/mL recorded <8 to 12[¥] weeks prior to delivery
High risk of HIV transmission at birth	▪ Mother on ART with unknown viral load <8 to 12 weeks prior to delivery or most recent HIV viral load was ≥1000 copies/mL ▪ Mother started ART <8 to 12 weeks prior to delivery or not on ART. ▪ Mother first diagnosed with HIV at delivery ▪ Mother has unknown HIV status
High risk of HIV transmission during breastfeeding.	▪ Mother on ART and most recent HIV viral load was ≥1000 copies/mL ▪ Mother not on ART (including mothers first diagnosed with HIV during breastfeeding)

[¥] 8 weeks applied to 2013 guidelines and 12 weeks to 2015 guidelines
Abbreviations – ART: antiretroviral therapy

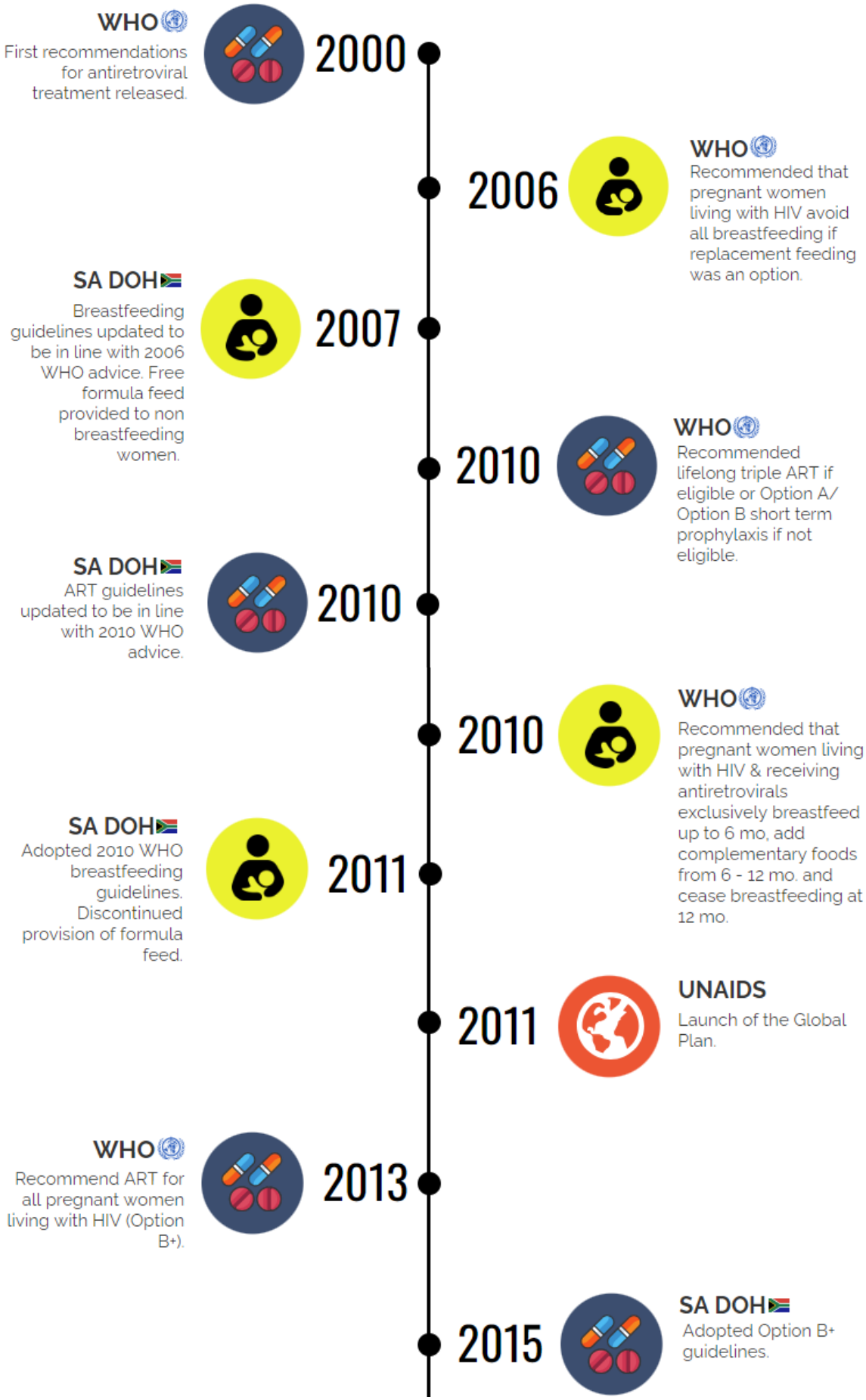
Breastfeeding:

Breastfeeding is known to play an important role in child development, health and survival (19,20,36). This importance is amplified in settings where children under the age of 5 commonly die from undernutrition, gastrointestinal and respiratory infections (37). Breastfeeding is protective against diarrhoeal and respiratory infections and could prevent an estimated 72% and 57% of related hospital admissions respectively (19). There is an increased risk of morbidity and mortality amongst children when substituting breast milk (19,20,38). Long term child and maternal health benefits as a result of breastfeeding for a longer duration have also been observed (20). Breastfeeding for a shorter duration, compared with breastfeeding for 5-6 months, increases the risk of death among infants (39).

In the absence of maternal antiretrovirals it was a challenge to promote HIV-free child survival while limiting the risk of vertical transmission of HIV (40). In 2006 (Figure 1.1), the WHO recommended that pregnant women living with HIV avoid all breastfeeding if replacement feeding was a viable option, but subsequently evidence showed that antiretroviral interventions could limit the vertical transmission of HIV during breastfeeding (41,42). 2010 saw a major shift when WHO infant feeding guidelines were updated to recommend that all pregnant women living with HIV, who are receiving antiretrovirals and have access to public health facilities, breastfeed their infants exclusively for the initial six months of life and continue to breastfeed with complementary foods up to 12 months of age (41). In the absence of antiretroviral access, HIV prevention was to be weighed up against the protection that breastfeeding could offer against non-HIV causes of death e.g. malnutrition and diarrhoeal disease. Moreover, national or sub-national authorities were to decide whether to collectively counsel women living with HIV to breastfeed alongside receiving antiretrovirals or not. This was in light of the fact that it would be feasible for women living with HIV to avoid breastfeeding in countries with low mortality and infectious disease rates (41).

In 2016, the recommended breastfeeding period for pregnant women living with HIV was extended to 24 months or beyond in the hope of improving survival among children who are HEU (20). This was in line with breastfeeding guidelines for people with a negative or unknown HIV status (20).

In SA, the 2007 Infant and Young Child Feeding (IYCF) policy recommended that pregnant women living with HIV exclusively breastfeed for up to 6 months followed by breastfeeding cessation, but (consistent with the 2006 WHO advice) avoid breastfeeding if replacement feeding was an option (43). Infant formula was provided, free of charge, to mothers who were not breastfeeding. The WHO's 2010 guidelines were adopted in SA in 2011 and the provision of infant formula was discontinued (44). In line with WHO guidelines, in 2017 the SA 2013 IYCF Policy was amended to recommend the breastfeeding period be extended to 24 months or longer (45,46). Figure 1.1 summarises the timeline of key global and SA policy changes described in this section.


WHO
First recommendations for antiretroviral treatment released.
2000
2006
WHO
Recommended that pregnant women living with HIV avoid all breastfeeding if replacement feeding was an option.
SA DOH
Breastfeeding guidelines updated to be in line with 2006 WHO advice. Free formula feed provided to non breastfeeding women.
2007
2010
WHO
Recommended lifelong triple ART if eligible or Option A/ Option B short term prophylaxis if not eligible.
SA DOH
ART guidelines updated to be in line with 2010 WHO advice.
2010
2010
WHO
Recommended that pregnant women living with HIV & receiving antiretrovirals exclusively breastfeed up to 6 mo, add complementary foods from 6 - 12 mo. and cease breastfeeding at 12 mo.
SA DOH
Adopted 2010 WHO breastfeeding guidelines. Discontinued provision of formula feed.
2011
2011
UNAIDS
Launch of the Global Plan.
WHO
Recommend ART for all pregnant women living with HIV (Option B+).
2013
2015
SA DOH
Adopted Option B+ guidelines.

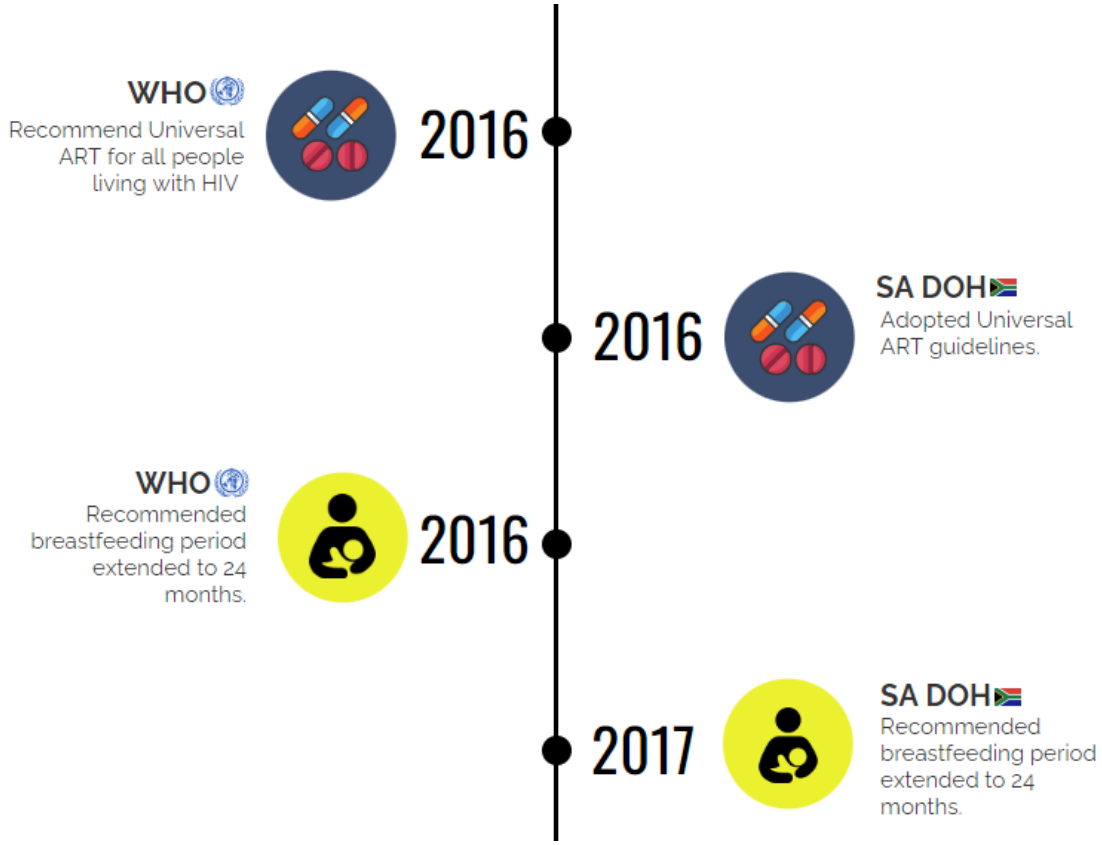


Figure 1.1: Timeline highlighting global and South African antiretroviral and breastfeeding policy changes.

Abbreviations – ART: antiretroviral therapy; DOH: Department of Health; mo: months; SA: South Africa; WHO: World Health Organisation

1.2.2. Prevention of vertical transmission of HIV

This section provides an overview of the burden of HIV among pregnant women and children at a global, SSA and SA level. Furthermore, it provides insight into the HIV VTP program and the success thereof, in line with the policy changes discussed above. The population statistics described in this section are those that are most recent, but, as the thesis describes children born until the end of 2018, I also show these statistics for 2017/2018 in Table 1.4.

In 2022, there were an estimated 39.0 million (uncertainty range: 33.1 – 45.7 million) people living with HIV worldwide (47). Among these, 20 million (uncertainty range: 16.9 – 23.4 million) were women ≥15 years of age and 1.5 million (uncertainty range: 1.2 – 2.1 million)

were children <15 years of age (47). In most cases children acquire HIV through vertical transmission (48). This could occur during pregnancy *(in utero*), birth or breastfeeding. However, with an effective HIV VTP program consisting of a continuum of interventions, the risk of vertical HIV transmission can be substantially reduced to below 5% (49–51). This continuum consists of: contraception to prevent unplanned pregnancies among women living with HIV, regular maternal HIV testing and counselling, lifelong ART for pregnant and breastfeeding women living with HIV, safe childbirth and suitable breastfeeding practices, and short-course post exposure prophylaxis for infants who are HEU (49).

In the last two decades, there has been a substantial scale-up and consequent success of the HIV VTP programme. Globally, new HIV infections among children have declined by an estimated 75% between 2000 and 2022: from 530,000/year (uncertainty range: 360,000 – 830,000) to 130,000/year (uncertainty range: 90,000 – 210,000) (52). Since 2000, an estimated 3.4 million new HIV infections in children have been prevented (53). This success has been largely attributed to the accelerated roll out of ART for pregnant women living with HIV (50).

Looking more specifically at SSA and SA, in 2011 when the Global Plan (Section 1.2.1) was launched an estimated 68% of all people living with HIV resided in SSA, with SA having one of the highest HIV prevalences among adults (15 – 49 years of age) at around 19.3% (uncertainty range: 17.0 – 21.2%) (54,55). The prevalence of HIV among pregnant women in SA was estimated at 29.5% (uncertainty range: 28.7 – 30.2%) in 2011 and had reduced slightly in 2022 (27.5%, uncertainty range: 27.0−28.1%) (56–58). In 2016, it was reported that the vertical HIV transmission rate among the Global Plan countries had dropped from 22.4% (uncertainty range: 19.8 – 25.4%) in 2009 to 8.9% (uncertainty range: 8.0 – 10.0%) in 2016 (59). More specifically, SA reduced the number of new vertical HIV infections by approximately 84% and its vertical transmission rate to an estimated ≤2% at birth and <10 weeks postnatal (59–61). SA has since achieved ≤750 vertical transmission cases per 100,000 live births (62). This is still above the elimination of vertical transmission goal of ≤50 cases per 100,000 live births (62).

With the reported prevalence of HIV among pregnant women in SA having been stable at around 30% from 2004 to 2019 (63), together with a declining vertical HIV transmission rate, the population of children HEU is growing substantially. Recent estimates from UNAIDS

reported that the population of children HEU in SA is estimated to be 4.1 million (uncertainty range: 2.7 – 5.2 million), having increased by over 450% between 2000 and 2022 (47). Although this growing population of children HEU may have escaped lifelong HIV infection, evidence suggests that they experience an increased risk of poor health outcomes in comparison to children HUU (7–12).

Table 1.4: Worldwide and South African population HIV statistics for 2017/2018

Indicator	Year of estimate	Estimate (uncertainty range)
Worldwide		
▪ Number of women ≥ age 15 years living with HIV	2018	18.8 million (15.9 – 21.9 million) (47)
▪ Number of children < age 15 years living with HIV	2018	1.9 million (1.5 – 2.6 million) (47)
▪ New HIV infections among children	2018	170,000/year (110,000 – 260,000) (47)
▪ Number of new HIV infections that have been averted	2017	2 million new HIV infections *No uncertainty range provided (64)
South Africa		
▪ Prevalence of HIV among pregnant women	2017	30.7% (30.1% − 31.3%) (63)
▪ Number of children HEU	2018	3.5 million (2.6 – 4.3 million) (3)

Abbreviations – HEU: HIV exposed uninfected

1.2.3. All-cause morbidity and mortality in children HEU vs. HUU (Pre-Option B+ ART: 2000 - 2013)

Much research was conducted in the pre-antiretroviral (i.e. before the year 2000) era to compare health outcomes in children HEU vs. HUU. Studies performed before HIV VTP strategies were widely implemented estimated that, although children HEU had better health outcomes than children with HIV, they had substantially higher mortality than children HUU (8,15,65,66). In this section, I present an overview of the evidence on all-cause mortality and

morbidity among children HEU relative to HUU in the Pre-Option B+ ART era, i.e. before 2013. All reported estimates are comparing children HEU to HUU (i.e. all children had a HIV-negative status), unless otherwise stated. For the purposes of this overview, only studies that were conducted post-2000 (when WHO first recommended the use of antiretrovirals for HIV VTP) and in SSA (where the prevalence of pregnant women living with HIV is highest) will be included. Studies conducted pre-2000 may be drawn on for contextual purposes.

1.2.3.1. Mortality

Three systematic reviews with meta-analyses published in 2016 all reported a pooled increased risk of mortality in children HEU relative to HUU (Table 1.5) (11,67,68). Table 1.5 provides a summary of the key differences (i.e. inclusion/exclusion criteria, timeframe, stratification criteria, and pooled estimates with 95% confidence intervals) between the three reviews.

Brennan *et al.* estimated an increased risk for all-cause mortality in children who were HEU compared to HUU, among participants that enrolled in studies included in their review in or after the year 2002 (when single-dose antiretrovirals were introduced in the majority of public sector clinics within African countries) (67). There was however evidence for a substantial level of statistical heterogeneity in this meta-analysis (I^2=74%). When shifting the enrolment completion cut off to 2004, to account for any potential delays in HIV VTP programme implementation, evidence of an increased risk in mortality remained.

Although there was an overlap between studies included in the Brennan *et al.* and Le Roux *et al.* meta-analyses, Le Roux *et al.* stratified their mortality analysis according to antiretroviral usage as opposed to year of enrolment (11). The majority of studies in which there was no/unknown maternal antiretroviral use were conducted prior to the year 2000. Only two studies (Shapiro *et al.* and Marquez *et al.)* were included in the sub-analysis of studies in which there was maternal use of 1 – 2 antiretrovirals and triple ART for women with advanced HIV (69,70). An increased risk for mortality in children HEU compared to HUU was observed in both studies and the meta-analysis. One of these two studies (Shapiro *et al.*) was also included in the Brennan *et al.* meta-analysis.

With very few studies reporting on maternal antiretroviral and breastfeeding practices, the Le Roux *et al.* review highlighted the inability of existing literature, at the time, to provide insight into health outcomes under current HIV VTP strategies. It was also noted by Le Roux *et al.* that, most often, studies had not been primarily designed to assess health outcomes in children HEU vs. HUU, with most studies including participants from intervention trials. As intervention trials have specific eligibility criteria and may provide participants with superior medical care, these participants may not accurately represent the general population (11). Furthermore, major confounders were often not accounted for in these secondary data analyses.

Arikawa *et al.* also found that the 12 and 24 month mortality risk estimates of children HEU were higher than that of children HUU (68). Very few studies (n=3 (39,66,71) and n=2 (66,70), respectively) were included in these pooled analyses, all of which were included in the analyses of Brennan *et al.* and Le Roux *et al.* described above.

In calculating comparable all-cause mortality outcomes, authors from all three reviews extracted raw data from the individual study reports and used this to calculate unadjusted risk ratios (uRiR) and 95% confidence intervals. The estimates in these meta-analyses therefore do not control for important confounders (e.g. socioeconomic status (SES) and maternal education). Estimates reported in these systematic reviews often differ from estimates reported in original studies for this reason.

A Botswanan study (Table 1.6, Study 0) not included in the above reviews, due to publication in the same year (2016) as the reviews, found that in comparison to children HUU those HEU were at greater risk of mortality by 24 months of age; adjusted hazard ratio (aHR)=2.70 (95% CI:1.60–4.50). Potential confounders such as maternal age and maternal education, but not SES, were controlled for in this analysis.

Table 1.5: Summary of systematic reviews assessing all-cause mortality in children HEU relative to HUU

Study	**Brennan *et al.* (2016)**	**Le Roux *et al.* (2016)**	**Arikawa *et al.* (2016)**
Objective	1. To assess differential all-cause mortality rates between children HEU and HUU (age not specified)	1. To assess differential all-cause mortality/morbidity in children HEU compared to HUU (age ≤10 years) 2. To investigate variation in any differences by breastfeeding practices and maternal ART usage	1. To assess differential all-cause mortality rates in children HEU compared to HUU (age ≤5 years) 2. To describe risk factors of mortality in children HEU
Inclusion and exclusion criteria	Inclusion: Studies (of any design) reporting on all-cause mortality in children HEU and HUU Exclusion: Not specified	Inclusion: ▪ Longitudinal studies reporting on mortality, diarrhoea, pneumonia, growth, or early developmental outcomes in children HEU ▪ Children who are HEU and had known negative HIV status ▪ Children HEU & HUU who were from similar settings or community ▪ Maternal HIV status determined by presence of HIV antibodies in children < 12 months Exclusion: ▪ Child HIV status not reported ▪ Case-control and cross-sectional study design ▪ Participants sampled based on maternal morbidity and child health (not HIV infection and exposure) ▪ Studies that have risk of bias > moderate	Inclusion: ▪ Studies of any design that reported all-cause mortality in children HEU ▪ Mothers with HIV and children without HIV, with no seroconversion Exclusion: ▪ Studies that reported case-specific mortality estimates ▪ Studies that did not report raw data (or data was not obtainable from the authors)
Timeframe	1994 – 2016	≤2015	2004 - 2015
Stratification criteria for meta-analysis:	Stratification by year of enrolment: 1. <2002 vs. ≥2002 2. <2004 vs. ≥2004	Stratification by maternal use of antiretrovirals: 1. No use vs. use of 1 – 2 antiretrovirals vs. use of 1 -2 antiretrovirals/triple ART	Stratification by child age: 1. At 12 months 2. At 24 months

Study		**Brennan *et al.* (2016)**	**Le Roux *et al.* (2016)**	**Arikawa *et al.* (2016)**
Type of meta-analysis:		Random effects	Random effects	Random effects
All-cause mortality estimates (HEU:HUU)		1. **≥2002 – RiR=1.46 (95% CI:1.14-1.87); (8 studies)** 2. ≥ 2004 **–** RiR=1.37 (95% CI:1.05-1.79); (number of studies not specified)	1. No use – RiR=1.78 (95% CI:1.03-3.10), (8 studies) 2. 1 – 2 antiretrovirals – RiR: 0.94 (95% CI:0.41-2.17), 3. (1 study) 4. **1 -2 antiretrovirals/triple ART – RiR=6.40 (95% CI: 1.99-20.62); (2 studies)**	1. **12 months – RiR=1.36 (95% CI:1.03-1.80),** 2. **(3 studies)** 3. **24 months – RiR=2.02 (95% CI:0.62-6.54),** 4. **(2 studies)**
Statistical heterogeneity (I^2)¥		74%	75%	1. 93% 2. 66%
Characteristics of included studies¥	**Locations:**	Malawi, SA, Tanzania, Uganda, Zimbabwe, Zambia	Botswana, Uganda	Botswana, Malawi, South Africa, Tanzania, Uganda, Zambia
	Sample sizes (ranges)	17 – 2091	671 – 2091	671 – 2125

Abbreviations: ART: Antiretroviral therapy; CI: Confidence Interval; HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected; RiR: Risk Ratio

¥Only statistical heterogeneity and characteristics of studies included in the sub meta-analysis resulting in the **bolded** mortality estimates are provided. I^2 refers to the proportion of total variation in estimates that is due to heterogeneity rather than chance

1.2.3.2. Morbidity

A systematic review by Slogrove *et al.* found conflicting results with respect to all-cause morbidity in children HEU compared to HUU (9). Of the 21 African studies included in the review, seven were conducted post the year 2000 and assessed all-cause morbidity. No meta-analysis was conducted as part of the review; I will therefore report on individual studies within the review. The Le Roux *et al.* review described in section 1.2.3.1 also reported the outcome of all-cause morbidity and included the same seven studies) (11). Details are provided in Table 1.6, studies 1 - 7. Studies were conducted in Botswana, Malawi, Mozambique and two each in SA and Uganda. Sample sizes ranged from 55 to 671 participants. Two of the studies (Table 1.6, studies 1 and 2) found no evidence of a difference in risk of morbidity between children HEU and HUU (69,72,73). The remaining five studies (Table 1.6, studies 3 - 7) indicated a potential increased risk in (all-cause) hospitalisations for children HEU relative to HUU (9,10,69,70,74,75), although this evidence was inconclusive for three of the studies (Table 1.6, studies 4, 6, 7) as the confidence intervals were wide, crossing the null (9,10,74,75). However, children HEU vs. HUU appeared to have a reduced risk of out-patient day visits (i.e. sick clinic visits) in two of these studies (Table 1.6, studies 4, 7) (75,76); again the confidence interval crossed the null for one of the studies (Table 1.6, study 7), rendering the estimate inconclusive.

In summary, despite inconsistencies, the literature most often suggests that during the early years of recommended antiretroviral use for HIV VTP there was still a potential increased risk of all-cause morbidity and of mortality in children HEU compared to their HUU counterparts. These estimates do however have to be treated with caution as in many of the studies confidence intervals were wide, crossing the null, meaning that the observed results are uncertain due to relatively small sample sizes.

Heterogeneity (both substantive and statistical) among studies makes meta-analyses results difficult to interpret. Substantive heterogeneity between the study outcomes observed may be due to several factors, namely: inconsistencies in maternal ART coverage or prevention of vertical HIV transmission prophylaxis use, differences in age profiles of infants/children followed up, region-specific differences in morbidity among children HEU, potential misclassification of HIV and antiretroviral exposure status, lack of comparability between

research groups of children HEU and HUU respectively (e.g. differing by socioeconomic status), and differences in infant feeding strategies (9,12,68). A further limitation is that the estimates reported in many of the above-mentioned studies were unadjusted for potential confounders. Any suggested associations between child HIV exposure status and increased child morbidity and mortality may therefore be biased due to confounding. The studies that did control for confounders (Table 1.6, studies 3 & 7) did however report estimates indicative of increased risk of hospitalisations and mortality among children HEU compared to HUU (69,76,77).

1.2.4. Infectious disease morbidity and mortality in children who are HEU vs. HUU (Pre-Option B+ ART: 2000 - 2013)

In this section, I present an overview of the available evidence, between the years 2000 and 2013, on infectious disease morbidity and mortality among children HEU relative to HUU, with a focus on two common infectious diseases: LRTIs and diarrhoeal diseases. All reported estimates are comparing children who have a negative HIV status, unless otherwise stated.

The majority of infectious disease related deaths occur in developing/resource limited settings, with an estimated 50% of pneumonia-caused deaths being in SSA (78). Malnutrition is considered an underlying risk factor for infectious disease morbidity and mortality and therefore, given that poverty is common in SSA countries, children are susceptible to infectious diseases regardless of HIV exposure status (79). Other risk factors include inadequate housing, overcrowding, poor access to clean water and sanitation, lack of access to healthcare services, and low parental educational status (80). It has been established that morbidity and mortality caused by diarrhoeal disease and pneumonia are prominent regardless of HIV exposure status, however, the risk factors are seen to occur more frequently among children HEU compared to HUU (9).

Sections 1.2.4.1 and 1.2.4.2 below refer to a 2019 systematic review and meta-analysis by Brennan *et al.* (13) as it includes many of the most recent studies in this field of research. Due to reasons discussed below, individual studies within the meta-analysis are focussed on for this overview. Therefore, ratio estimates from the primary studies will be reported here. If ratio estimates were not provided in the primary study, I will report the (unadjusted)

estimates used in the Brennan meta-analysis. Estimates that are adjusted (a) and unadjusted (u) for confounders will be distinguished.

1.2.4.1. Diarrhoeal Disease

Diarrhoea is defined by the WHO as "the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)" (81). Yearly there are an estimated global 1.7 billion cases of diarrhoeal disease among children, of which an estimated 443,832 are fatal in children under the age of five, making diarrhoea the third highest cause of death in this age-group of children (81). In 2016, almost 90% of diarrhoea-related deaths occurred in SSA and South Asia (82).

Brennan *et al.* estimated that, over 5 years, children HEU compared to HUU were 1.36 (uRiR, 95% CI: 0.91-2.03) times more likely to have acute diarrhoea, based on a meta-analysis of 7 studies (13). This pooled effect estimate was imprecise due to inconsistencies in the results of studies included in the meta-analysis (i.e. statistical heterogeneity) (I^2=74%). Moreover, two of the studies included in the meta-analysis were based on data collected before the year 2000. Thus, in this overview ,I focus on five of the seven studies included in the Brennan meta-analysis of acute diarrhoea outcomes (Table 1.6, studies 2, 3, 5, 7, 8). Four of these studies (studies 2, 3, 5, and 7) were included in the Le Roux *et al*. and Slogrove *et al.* reviews discussed above.

Of the five studies of interest, two, conducted in Malawi and Botswana (Table 1.6, studies 2, 5) estimated no increased risk of diarrhoea in children who were HEU vs. HUU (estimates reported by Brennan *et al.)* (13,70,73). Of the remaining three studies, a study in Uganda (Table 1.6, study 3) observed a substantially higher risk of severe diarrhoea among 6 - 11 month old, non-breastfed children HEU vs. breastfed children who were HUU (13,69). In the fourth study, by Rollins *et al.,* (Table 1.6, study 8) evidence with regards to the risk of overall diarrhoea, in the first six months of life, in breastfed children HEU compared to HUU, was inconclusive (39). In an additional SA study (Table 1.6, study 7), there was no evidence of a difference in the estimated risk of diarrhoea-related sick clinic visits for children HEU and HUU (76). However, the proportion of children HEU (9%) hospitalised for diarrhoea compared to HUU (1%) was estimated to be higher (P<0.05). This suggests that the children who were HEU may have been experiencing more severe diarrhoea, hence more hospitalisation cases.

In summary, no definite conclusions can be drawn on whether there was a difference in infectious morbidity due to diarrhoea between children HEU and HUU, during Pre-Option B+ ART (and post the year 2000). Studies suggest that there may have been an increased risk for hospitalisation due to severe diarrhoea in children HEU compared to HUU. However, as noted by Slogrove *et al.*, diarrhoeal disease is complexly linked to infant breastfeeding practices. This makes it difficult to distinguish suboptimal breastfeeding and HIV exposure as risk factors for diarrhoea-caused morbidity and mortality (9,69,76). Furthermore, several studies (Table 1.6, studies 2, 5 and 7) did not control for confounders in their analyses, potentially biasing outcome estimates.

1.2.4.2. Respiratory infections

Respiratory infections are one of the leading causes of death among children under the age of 5 (83). Pneumonia, a common LRTI, accounts for an estimated 14% of under-5 global child deaths, being responsible for 740,180 child deaths in 2019 (84). Studies have reported a high burden of LRTIs among all infants (9,85,86). However, results comparing the burden in children who are HEU to HUU have varied. Below I report on studies that assessed outcomes defined more broadly as LRTIs or more specifically as a type of LRTI, e.g. pneumonia.

The 2019 meta-analysis by Brennan *et al.* reported children HEU to have an estimated 31% (uRiR=1.31, 95% CI:1.13-1.53) increased risk of pneumonia over 5 years of follow-up compared to children HUU (13), based on six studies. However, of these six studies, two were conducted on data prior to the year 2000. Of the other four studies, one (Table 1.6, study 12) observed no difference in pneumonia prevalence (87) by HIV exposure status (ratio estimate reported by Brennan *et al.*) (13). The other three studies (Table 1.6, studies 5, 7, 10) estimated an increased risk of pneumonia in children HEU vs. HUU, although all three confidence intervals were wide, crossing the null. (13,70,76,85). Only one of these four studies controlled for potential confounders of the HIV exposure and infectious disease outcome relationship and as a result estimates may be biased.

A study which was not included in the meta-analysis due to not specifically assessing pneumonia outcomes (Table 1.6, study 4) suggested a decreased risk of respiratory tract infections in children HEU relative to HUU (75). In this study from Mozambique, there was evidence suggesting that children HEU were less likely to have had outpatient hospital visits

due to a) acute upper respiratory tract infections and b) acute lower respiratory tract infections, compared to children HUU, up to 12 months of age (75). On the contrary, a follow-on study by Le Roux *et al.* (Table 1.6, study 11), as well as another SA study by Cohen *et al.*, (Table 1.6, study 9) reported that children HEU vs. HUU had an estimated higher incidence of hospitalisation for LRTI up to 6 months of age (86,88). Children who were HEU and hospitalised with LRTIs also had an elevated risk of dying in hospital than children who were HUU (88). Again, very few of the reported estimates were adjusted for potential confounders.

1.2.4.3. Summary

In summary, there is a substantial burden of infectious disease among infants, irrespective of HIV exposure. Evidence during the Pre-Option B+ ART era suggests that no clear conclusions can be drawn with respect to whether children HEU vs. HUU are at an increased risk of diarrhoeal and respiratory disease, mainly due to inconsistencies in study results. Studies do, however, suggest increased risk of hospitalisations due to more severe cases of diarrhoea and LRTIs in children HEU compared to HUU. Although some studies reported on breastfeeding and prophylaxis use, this was not done consistently. As described in Section 1.2.1, guidelines on ART and breastfeeding have also been updated since these studies were conducted. It is therefore of interest to assess the risk difference for infectious morbidity and mortality between children who are HEU and HUU in the Option B+ and Universal ART eras.

Table 1.6: Summary of studies comparing all-cause morbidity and/or mortality and infectious disease outcomes in children HEU vs. HUU under pre-Option B+ guidelines

No.	Author [year] (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: Children HEU vs. HUU point estimate (95% CI)/ proportions	Factors adjusted for in point estimates	Study limitations
Studies reporting on all-cause mortality (not included in systematic reviews)										
0.	Zash [2016] (77)	Botswana (2012 – 2013)	Prospective cohort (1515*:1518) *Includes children who are HEU and children with HIV	During pregnancy: ART: 58% Zidovudine: 23% No antiretrovirals: 11% Unknown: 8%	Children who were: HIV-exposed: 16% HUU: 98%	Child mortality; risk factors for mortality	Up to 24 months	**Mortality:** aHR=2.70 (95% CI: 1.60-4.50) *Estimate did not distinguish children who were HEU and children with HIV	Infant congenital abnormalities, infant birth injuries, preterm delivery, breastfeeding practice, season of birth, water access, maternal education, maternal age, parity, maternal marital status, ART regimen	Sample included lower risk infants – potential underestimation of mortality Potential confounding due to unmeasured sociodemographic factors HIV status of majority of infants who died < 6 weeks unknown
Studies reporting on all-cause morbidity and (diarrhoea and/or pneumonia)										
1.	Homsy [2014] (72)	Uganda (2007 – 2008)	Secondary analysis of a RCT – prolonged infant co-trimoxazole exposure (CTX) (185:100)	Not reported	**Any breastfeeding:** Children: HEU: 100% HUU: 100%	Secondary objective: Diarrhoeal illness, respiratory tract infections, hospital admissions & adverse events	Up to 48 months	No difference in the rate of any outcome events in children HEU vs. HUU (estimates not reported)	None	Study primarily designed to measure malaria incidence by co-trimoxazole exposure status – important confounders for the secondary objective not accounted for Self-reporting of co-trimoxazole adherence– potential respondent bias
2.	Landes [2012] (73)	Malawi (2008)	Retrospective cohort (173:214)	Maternal ART before delivery: 10% Maternal ART by 18 – 20 months post-partum: 27%	**Exclusive (opted):** Women living with HIV: 20% Women living without HIV: 1%	Child mortality; hospital admissions and diarrhoeal episodes	Up to 20 months	**Child mortality at 20 months:** Children HIV-Exposed* (19%) vs. HUU (4%) *Doesn't distinguish	None	Substantial loss to follow-up - potential bias and underestimation of mortality Health outcomes only reported on children surviving to 20 months – survival bias Small sample size

No.	Author [year] (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: Children HEU vs. HUU point estimate (95% CI)/ proportions	Factors adjusted for in point estimates	Study limitations
				NVP maternal prophylaxis: 75%	Breastfeeding >18 months: Children who were HEU:HUU (mixed breastfeeding) - 48:90%			children with and without HIV among those who are exposed. **All-cause morbidity:** estimates not reported **Diarrhoea episodes:** Children HEU: 49 (40-58) % HUU: 57 (50-64) % (no statistics for comparison reported)		Data collected retrospectively – recall bias Maternal health not reported on in terms of CD4 count and viral load Mortality estimates don't distinguish children with and without HIV among those that are exposed
3.	Marquez [2014] (69)	Uganda (2010 – 2011)	Secondary analysis of a malaria regimen RCT (186: 389)	**Based on maternal report:** Antenatal ART: 35% Perinatal ART: 78%	Had to be breastfeeding to be included in the study and were then counselled as per the guidelines. **Children HEU vs. HUU:** 6 months: 84% vs. 99% 12 months: 29% vs. 99% 24 months: 0% vs. 24%	All-cause hospitalisation, non-malaria associated hospitalisation, severe febrile illness/ pneumonia, severe diarrhoea	Up to 24 months	**Mortality:** uRiR=13.70 (95% CI:1.12–167.3) **Morbidity:** **Non-breastfeeding children HEU vs. HUU (6-11 months):** All hospitalisations: aRiR=10.10 (95% CI: 3.70-27.60) Severe diarrhoea: aRiR=6.37 (95% CI: 2.32-17.4)	**Morbidity:** **Non-breastfeeding children who were HEU vs. breastfeeding children who were HUU (6-11 months):** Maternal age, chemoprevention, wealth index **Non-breastfeeding children HEU vs. non-breastfeeding HUU (12- 24 months):** Maternal age, chemoprevention, wealth index	Small sample size Children in study had better access to healthcare than the general population Uncertainty surrounding HIV exposure status

No.	Author [year] (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: Children HEU vs. HUU point estimate (95% CI)/ proportions	Factors adjusted for in point estimates	Study limitations
								Non-breastfeeding children HEU vs. non-breastfeeding children HUU (12-24 months): All hospitalisations: aRiR=0.97 (95% CI: 0.54-2.43) Severe diarrhoea: aRiR 2.21 (95% CI: 0.79-6.16)		
4.	Moraleda [2014] (75)	Mozambique (2008 – 2009)	Prospective cohort (158: 160)	**Maternal ART before delivery:** 13%	**Any breastfeeding:** Similar in children HEU & HUU until 6 months (estimates not given) **12 months:** Children HEU: 53% HUU:100%	Outpatient department (OPD) visits, hospital admissions	Up to 12 months	**OPD visits:** Overall: uIRR=0.79 (95% CI: 0.63-0.99) Diarrhoea: uIRR=0.50 (95% CI: 0.54-0.86) URTI: uIRR=0.71 (95% CI: 0.51-0.99) LRTI: uIRR=0.77 (95% CI: 0.53-1.11) **Hospital admissions:** Overall: uIRR=1.51 (95% CI: 0.71-3.18) Diarrhoea: uIRR=0.93 (95% CI: 0.19-4.62)	None	Small sample size Those needing urgent medical care at birth weren't included – potential selection bias

No.	Author [year] (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: Children HEU vs. HUU point estimate (95% CI)/ proportions	Factors adjusted for in point estimates	Study limitations
5.	Shapiro [2007] (70)	Botswana (2003)	RCT based cohort study (534:137)	zidovudine + Sd NVP	**Median duration:** Women living with HIV: 6 months Women living without HIV: 9 months **Exclusive breastfeeding at 5 months:** Women living with HIV: 18% Women living without HIV: 10%	Morbidity and mortality (mortality: hospitalisations, diarrhoea, respiratory illness)	Up to 24 months	**Outcome proportions (children HEU: children HUU)** **At 6 months:** Pneumonia: 10%: 8% (P=0.43) Diarrhoea: 32%: 34% (P=0.72) Hospitalisations: 13%: 5% (P=0.002) Death: 4%: 1% (P=0.01) **24 months:** Pneumonia: 18%: 11% (P=0.03) Diarrhoea: 66%: 57% (P=0.08) Hospitalisations: 21%: 10% (P=0.004) Death: 7%: 2% (P=0.002)	None	Small sample size Potential uncertainty surrounding HIV exposure status
6.	Slogrove [2012] (10)	South Africa (2012 – 2014)	Prospective cohort (27:28)	**Maternal:** None: 11% Combination ART: 15% Prophylaxis: 70%	**Any Breastfeeding:** Children HEU: 4% HUU: 100%	Infectious disease hospitalisation	Up to 12 months	**Sick-clinic visits:** uIRR=1.06 (95% CI: 0.79-1.39) **Hospitalisation (infectious-cause):** uIRR=2.74 (95% CI: 0.75-8.78)	None	Small sample size No data on SES – Potential confounding Potential hospitalisation admission bias as clinicians were aware of HIV-exposure status

No.	Author [year] (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: Children HEU vs. HUU point estimate (95% CI)/ proportions	Factors adjusted for in point estimates	Study limitations
7.	Slogrove [2017] (76) *representative of the results of Slogrove [2015] (74) (thesis)	South Africa (2012 – 2013)	Prospective cohort (94:82)	**Maternal:** 50% (n=47) received maternally indicated ART 43% (n=20) of those on ART initiated ART before pregnancy	**Median duration:** 112 days for children HEU & HUU **Intention to exclusively breastfeed:** Children HEU: 39% HUU: 98% **Exclusive breastfeeding** At 2 weeks: Children HEU: 34% HUU: 82% At 6 months: Children HEU: 6% HUU: 5%	**Primary:** Hospitalisation for infection or death <194 days **Secondary:** severe/very severe hospitalisation or death	Up to 6 months	**All-cause sick-clinic visits:** uRR=0.82 (95% CI: 0.58-1.16) **Hospitalisation (infectious-cause):** aOR=1.45(95% CI: 0.44-4.45) **Hospitalisation (severe):** aOR=1.61 (95% CI: 0.48-5.09) **Hospitalisation (very severe):** aOR=2.49 (95% CI: 0.60-10.19) **Hospitalisation among breastfed (very severe):** aOR=4.20 (95% CI: 1.00-19.20)	**All hospitalisation models (irrespective of breastfeeding):** Maternal age, any breastfeeding at two weeks **Hospitalisation among breastfed (very severe):** Maternal age	Only included low risk mothers and infants Small sample size Controlled for factors which could be on the causal pathway: (in estimates other than those reported here) breastfeeding, low birth weight, preterm birth, CD4
Studies reporting on diarrhoea-specific morbidity										
8.	Rollins [2013] (39)	South Africa (2001 – 2005)	Intervention cohort study (1082*: 1155) *Includes infants with and without HIV. By 6 months of age 936 of these infants were without HIV	Only sd NVP was available for prevention of vertical HIV transmission	**Mothers with HIV: Mothers without HIV** Any breastfeeding: (73%: 80%) **Exclusive:** 6-8 weeks: (81%: 93%) 3-4 months: (62%: 73%)	Diarrhoea, all-cause mortality	Up to 18 months	**Diarrhoeal events (first 6 months):** aHR=1.45 (95% CI: 0.75-2.79) **Mortality (first 12 months):** aHR=0.77 (95% CI:0.49-1.21)	**Diarrhoeal events (first 6 months):** Feeding practice, sex, water source, enrolment clinic **Mortality (first 12 months):** Feeding practice, sex, water source, enrolment clinic	Relied on mothers' self-report – but is at least once a week

No.	Author [year] (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: Children HEU vs. HUU point estimate (95% CI)/ proportions	Factors adjusted for in point estimates	Study limitations
Studies reporting on respiratory tract-specific morbidity										
9.	Cohen [2016] (88)	South Africa (2010 – 2013)	Prospective cohort (850:1446)	Not reported	Not reported	Hospitalisation for LRTI, a) overall & b) by viral etiology Mortality	Up to 6 months	**All LRTI hospitalisation:** uIRR=1.40 (95% CI: 1.30-1.50) **Mortality:** aRiR=2.10 (95% CI: 1.10-3.90)	**Mortality:** Age, race, hospital, year of hospitalisation, RSV coinfection, length of hospital stay, admission to intensive care vs. mechanical ventilation vs. oxygen required	No data on maternal ART use, CD4 cell count, and breastfeeding. Relied on maternal report to determine maternal HIV status in >70% of participants Unmeasured confounding e.g. SES status Because enrolling based on having a LRTI those who die are less likely to be enrolled – selection bias LRTI only measured at 1 site – small sample size, limits generalisability Mode of denominator calculation may have introduced bias
10.	D. Le Roux [2015] (85)	South Africa (2012 – 2014)	Prospective cohort (130:567)	Not reported	**Never breastfed:** Site 1: 9% Site 2: 31% **Exclusively breastfed for 6 months:** Site 1: 9% Site 2: 13% *Proportions are overall and not specific to exposure status.	Pneumonia episodes	Up to 12 months	Pneumonia: aIRR=1.55 (95% CI: 0.81-2.96) Severe pneumonia: aIRR=4.04 (95% CI: 1.51-10.80)	Pneumonia: Site of enrolment, sex, feeding practice, child age Severe pneumonia: Site of enrolment	Study not primarily designed to compare children HEU to HUU - Confounders not controlled for Questionnaires administered – potential recall bias HIV testing not reported – potential misclassification of exposure and infection status

No.	Author [year] (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: Children HEU vs. HUU point estimate (95% CI)/ proportions	Factors adjusted for in point estimates	Study limitations
11.	D. Le Roux [2019] (86)	South Africa (2012 – 2017)	Longitudinal cohort study (894:247)	**Maternal:** Triple ART: 73% (n=180) Short term ARV prophylaxis: 28% (n=69)	**Median duration of exclusive breastfeeding:** 1.84 (95% CI: 0.92-4) months **Never breastfed:** 10% **Breastfed ≥ 6 months:** 14%	LRTI	Up to 2 years	**Hospitalisations:** <6 months: uIRR=1.99 (95% CI: 1.11-3.54) 6-12 months: uIRR=1.26 (95% CI: 0.44-3.60)	None	Study not primarily designed to compare children HEU to HUU - Confounders not controlled for Potential misclassification of exposure and infection status
12.	Luabeya [2007] (87)	South Africa (2003 – 2004)	RCT Treatment: Vitamin A/ vitamin A + zinc/ vitamin A + zinc + micronutrients (154:187)	Not reported	Most infants receive breast and complementary feeding (estimate not given)	Infectious illness: diarrhoea, pneumonia	6 to 24 months	**Chronic diarrhoea:** uRiR=1.08 (95% CI: 0.99-1.22) **Pneumonia:** uRiR=1.05 (95% CI: 0.59-1.87)	None	Study not primarily designed to compare infectious disease by HIV exposure status – important confounders not accounted for

Abbreviations – a: adjusted; ANC: antenatal care; ART: antiretroviral therapy; ARV: antiretroviral; CI: confidence interval; HEU: HIV-exposed uninfected; HUU: children HIV-unexposed uninfected; HR: hazard ratio; IRR: incidence rate ratio; LRTI: lower respiratory tract infection; NVP: nevirapine; OPD: outpatient department; OR: Odds Ratio; PCR: polymerase chain reaction; PR: prevalence ratio; RCT: randomised control trial; RiR: risk ratio; RR: rate ratio; u:unadjusted; URTI: upper respiratory tract infection; RSV: Respiratory syncytial virus; Sd: single-dose; SES: socioeconomic status; VTP: vertical transmission prevention

1.2.5. Evidence under Option B+ and Universal ART guidelines

This section gives an overview of the evidence on all-cause mortality and infectious disease morbidity in the context of more recent ART and breastfeeding guidelines.

1.2.5.1. All-cause mortality

In Zimbabwe, a secondary analysis of data from the Sanitation, Hygiene, Infant, Nutrition Efficacy (SHINE) trial (Table 1.7, study 13) found that in a setting with high antenatal HIV prevalence, high exclusive breastfeeding rates and good coverage of HIV VTP programmes (>80%), children exposed to HIV were at an estimated 40% higher risk of mortality compared to those HUU; aHR=1.41 (95% CI: 1.02-1.93) (adjusted for trial arm) (89). Half of the deaths occurred by 9 days of age. They also observed that among children who were HIV-exposed, those whose mothers were on ART during pregnancy vs. not on ART had a lower estimated risk of mortality. Furthermore, mortality was estimated to be similar among children who were ART-exposed and those unexposed to HIV; uHR=1.11 (95% CI: 0.7–1.65). It should be noted, however, that of the children who were HIV-exposed and died, 90% had an unknown HIV status (due to having not been HIV tested). It is therefore uncertain whether increased mortality was due to HIV transmission or exposure.

A SA study (Table 1.7, study 14) among very low birth weight (VLBW) neonates (<1500g) estimated an increased mortality risk in neonates who were exposed to HIV compared with those HUU; aOR=1.39 (95% CI: 0.99–1.97) (90). The authors further estimated that the increased risk of mortality was reduced when restricting analysis stratifying to infants with a birth weight ≥1000g and strengthened among those born <1000g, indicating an interaction between HIV exposure status and birth weight. This study did not distinguish between neonates living with or without HIV among those who were HIV-exposed. Measures of association may therefore be overestimates of the HEU vs. HUU risk.

A secondary analysis of Malawi Demographic and Health Surveys data (Table 1.7, study 15) reported a change in the association between infant HIV exposure status and perinatal mortality between 2010 and 2015 (91). Infants who were HIV-exposed (those living with and without HIV were not distinguished) compared to HUU had an increased risk of mortality in

2010; adjusted odds ratio (aOR)=1.50 (95% CI: 1.10–3.10), whereas there was no estimated excess risk in 2015. The observed changes in effect estimate could be due to the success of the scale-up of HIV VTP programmes and the introduction of Option B+. In SA, an analysis of data from the Infant Burden Study (Table 1.7, study 16), observed no increase in the risk of in-hospital mortality among children HEU compared to HUU, whereas the risk was substantially higher among children with HIV vs. those HUU; aOR=4.79 (95% CI: 1.49–15.37) (92). Together, these study results suggest that during an era of increased access to maternal ART, it is possible that an increased risk of mortality remains for children with HIV, but not children HEU, compared to those HUU. Further studies are however required to explore this further.

1.2.5.2. Infectious morbidity

A multicentre longitudinal study in SA and Nigeria during the Option B+ and early Universal ART period (2013 -2017) (Table 1.7, study 22), estimated that there was no difference in infectious disease incidence among children HEU vs. HUU; aHR=1.01 (95% CI: 0.78-1.32). This estimate was adjusted for maternal education level and occupation, maternal CD4 count at delivery, infant birth weight, gestational age at birth, feeding practice, clinical site, and Cotrimoxazole use (93). The researchers also found that exclusive breastfeeding was estimated to be protective against infectious diseases when compared to formula feeding, with the same effect being observed when comparing mixed feeding to no breastfeeding. Although it may seem that breastfeeding alleviates the increased risk caused by maternal HIV exposure, these results should be treated with caution. The study was conducted in a low risk group of infants (excluding infants born preterm, or low birth weight (LBW), subject to pregnancy/birth complications, and with known tuberculosis contacts). Results can therefore not be generalised to the population of children who are HEU and born preterm, with preterm birth being a risk factor for infectious outcomes (94). The study also defined infectious morbidity as sick-clinic visits, hospitalisations and mortality and, given that pre-Option B+ studies also observed no risk difference/reduced risk in sick clinic visits by HIV exposure status (HEU:HUU), it is possible that infectious morbidity may differ in severity between children who are HEU and HUU (94).

A WC cohort study by Le Roux *et al.* during the Option B+ era (2013-2015) (Table 1.7, study 21), mentioned in the thesis introduction, reported that, although hospital admission rates were observed to be highest in both groups in the first seven days of life, infection-related hospitalisations were estimated to be more common among infants who were HEU (34.2 admissions/100 child-years) compared to HUU (9.8 admissions/100 child years), unadjusted incidence rate ratio (IRR)=3.50 (95% CI: 1.68-7.30), between the first 8 days and 3 months of life (17). Interestingly, this difference was seen to be ameliorated (although an imprecise estimate) when only considering infants who were HEU and whose mothers were deemed healthier (CD4 count >350 cells per µL, HIV viral load <4.0 log_{10} copies per mL and started ART <24 weeks gestation). Infants born to women living with HIV with late ART start (≥24 weeks gestation) and more severe HIV (CD4 count ≤350 cells per µL and HIV viral load ≥4.0 log_{10} copies per mL) had the highest estimated risk, in this age group, compared to children who were HUU; aIRR=5.01 (95% CI: 1.50-16.71). This estimate was adjusted for access to running water, a flushing toilet, preterm birth, maternal postpartum depression, low birth weight, season at birth, breastfeeding practice and vaccination completion. LRTI (43%) and diarrhoea (24%) were the most common causes of infectious disease hospital admissions of which the prevalence was suggested to be higher in children HEU compared to HUU. In addition, a more recent publication by Le Roux *et al*. reported that excess risk of poor health outcomes among children HEU may be driven by maternal HIV-related syndemics (95); they observed an interaction with maternal HIV and household food insecurity on infection-related hospitalisation between 7 days and 3 months of life.

The Le Roux *et al.* study (Table 1.7, study 21) too has limitations. It was conducted in a relatively small cohort linked to a single Midwife Obstetric Unit (MOU) within Cape Town. Results may therefore not be generalisable to the wider WC or SA population. Furthermore, the study did not include women living with HIV that initiated ART before conception. With the scale up of lifelong Universal ART, it is likely that women will be conceiving on ART. While ART exposure before pregnancy should allow for mothers to be healthier from the start of pregnancy and thus reduce infectious disease risk in their infants, ART exposure in the first trimester may be associated with pre-term birth and other adverse birth outcomes (discussed in section 1.2.6.3) which could increase risk of infectious diseases. It is therefore important to investigate the health outcomes in this group of children HEU. In addition, infants who were

censored before 48 weeks of age were reported with the HIV status that was determined at their 6-week HIV test. It is possible that some of these infants may have acquired HIV post their 6-week test and there is therefore uncertainty surrounding infant HIV status.

Another WC study during the Option B+ era (2012-2015) by Wedderburn *et al.* (Table 1.7, study 23) showed increased rates of all-cause hospitalisation in children HEU vs. HUU up to age 1 year; aHR=1.54 (95% CI: 1.19-2.00), but not between age 1 and 2 years; aHR=0.91 (95% CI: 0.53-1.55) (23). LRTIs (39%) and gastroenteritis (18%) were the most common causes of admission. The risk of hospitalisation due to gastroenteritis was higher in children HEU vs. HUU; uOR=2.35 (95% CI: 1.36-4.04). Length of hospital admission was also longer for children HEU compared to HUU. Furthermore, they observed that breastfeeding was protective against hospitalisation, particularly hospitalisation due to gastroenteritis, and that delay in vaccination increased the risk of hospitalisation among all children aged 0-12 months. A maternal HIV viral load of >40 copies/mL during the antenatal period also increased the risk of admission among children HEU aged 6–12 months. Study limitations included potential missing hospitalisations and low breastfeeding rates.

Anderson *et al.* published two papers comparing infection-related hospitalisation in children HEU vs. HUU in the WC during the Universal ART era (2017-2018) (Table 1.7, studies 17 and 18) (24,96). The first paper reported that proportions and rates of hospitalisation were similar for neonates (0-28 days) HEU and HUU; 5 vs. 6% (P=0.47) and aOR=0.65 (95% CI: 0.33-1.25) (96). This adjusted estimate was controlled for maternal education, maternal age, infant multiple pregnancy status and housing. They also found that, among hospitalised neonates, those HEU, compared to HUU, had higher risk of admission to the intensive care unit (ICU); uRiR=2.05 (95% CI: 1.28-3.30). This suggests more severe infectious morbidity in children HEU compared to HUU during the neonatal period. In their second paper, Anderson *et al.* focussed on the postneonatal period up to age one year (24). They observed an increased risk of infection-related hospitalisation in children HEU vs. HUU (aIRR=2.84, 95% CI:1.49-5.39) after adjusting for the confounders listed above for the first paper, in addition to vaccination status. Despite breastfeeding reducing the risk of infection-related admissions, the increased risk of admission remained in children HEU vs. HUU when restricting to children who were breastfed for ≥3 months. Up to date vaccination was protective against infection-related hospitalisation. Anderson *et al.* acknowledged potential residual confounding and HIV infection and exposure

status misclassification in their analyses. An additional limitation is that they didn't have records of out-of-province admissions and deaths as well as out-of-facility deaths. If these differed by HIV exposure status they may have biased observed results. Furthermore, participants in their study were enrolled from a single primary healthcare facility in a lower income urban area of the WC. Their results are therefore not generalisable to rural WC or SA.

Although I've mainly reported on studies from low-and-middle income countries (LMICs), I consider here a study from a higher income country (Belgium) (Table 1.7, study 19) (97). This study reported several important findings. Firstly, even with Universal ART there was an increased risk of infectious hospitalisation in children who were HEU vs. HUU, aHR=2.33 (95% CI: 1.10-4.97). This estimate was adjusted for birth weight, gestational age, literacy, maternal education, maternal African origin, maternal age, primiparity. Secondly, this estimate was attenuated when restricted to mothers who initiated ART before pregnancy; aHR=1.42 (95% CI: 0.58-3.48), and increased when restricted to mothers who initiated ART during pregnancy; aHR=3.84 (95% CI: 1.69-8.71). This suggests timely initiation of ART could potentially substantially ameliorate the excess risk of infectious disease faced by children HEU. Thirdly, the study found that immune alterations, such as monocyte activation and decreased maternal antibody transfer, were most intense among children HEU whose mothers initiated ART during pregnancy as compared to before pregnancy and that these alterations were predictive of clinical outcomes. This highlighted the potential for the use of immune biomarkers to identify infants at risk of severe infections which could guide preventative interventions. This study was restricted to a single site and conducted in a small sample, potentially limiting the generalisability of the results. The proportion of children breastfed differed between children who are HEU and HUU, $p<0.001$ (no children who were HEU were breastfed, as per European guidelines), although duration of breastfeeding was not associated with increased risk of hospitalisation in children HUU.

Another high-income country (United States) study by Labuda *et al.* reported an increased risk of first infectious disease; uIRR=2.31 (95% CI: 2.02-2.64), and total infectious disease hospitalisations; uIRR=2.17 (95% CI: 1.92-2.44), in children HEU compared to HUU (98). Furthermore, they found that gastroenteritis and bronchiolitis occurred more often in children HEU vs. HUU. In this study, data for children HEU and children HUU were collected using different studies/methods. The data for children HUU didn't include data on important

confounders such as SES and maternal age; consequently, these confounders could not be controlled for in the analysis.

The results from these two studies suggest that even in high-income countries children HEU are at risk of suboptimal health outcomes compared to children HUU. Contrary to LMICs, women living with HIV in high-income countries are encouraged not to breastfeed. In addition, there are factors in LMICs that are likely associated with infectious disease outcomes and are less of a concern in high-income settings, e.g. sanitation and hygiene practices, overcrowding, and number of immunocompromised individuals per household.

1.2.5.3. Summary

All-cause mortality studies that were conducted during the Option B+ and Universal ART periods found that, although excess mortality exists among HIV-exposed infants (some of whom are potentially living with HIV) compared to HUU, this excess is reduced among children exposed to maternal ART (89,91). Another study showed no increased risk of in-hospital mortality in children HEU vs. HUU, but a substantial increase when comparing children with HIV to those HUU (92). Children HEU are likely exposed to maternal ART and it's therefore possible that a substantial portion of the excess risk of mortality among children HIV-exposed is among those living with HIV. The available evidence on infectious disease outcomes suggests that there is an increased risk of infection-related hospital admissions among children HEU compared to HUU during the Option B+ and Universal ART eras. Furthermore, the evidence suggests that timely ART initiation, optimal breastfeeding practices and child vaccination could potentially mitigate some of the infectious disease risk difference observed between children HEU and HUU (17,23,24,97). However, future larger longitudinal cohort studies in high HIV prevalence settings are required to further understand this relationship (99).

Table 1.7: Summary of studies comparing a) all-cause morbidity and mortality and b) infectious disease outcomes in children HEU vs. HUU under Option B+ and Universal ART guidelines

No	Author, [year], (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: children HEU vs. HUU point estimate (95%CI)/ proportions¥	Factors adjusted for in point estimates	Study limitations
Studies reporting on all-cause mortality										
13.	Evans [2020] (89)	Zimbabwe (2013 – 2015)	Secondary analysis of a RCT (738*:3989) *Does not distinguish between children with and without HIV	**Maternal ART during pregnancy:** 81%	**Exclusive breastfeeding at 6 months:** No difference between groups (data not shown)	Mortality	Up to 18 months	Overall mortality**:** aHR=1.41 (95% CI: 1.02-1.93) * children with HIV and children HEU not distinguished ART-exposed vs. ART-unexposed**:** aHR=0.41 (95% CI: 0.22-0.76) ART-exposed vs. HUU: aHR=1.11 (95% CI: 0.75-1.65) ART-unexposed vs. HUU: aHR=2.74 (95% CI: 1.69-4.44)	Trial arm	Could not determine HIV status in majority of children who died Important confounders not adjusted for Does not distinguish children with HIV and without HIV, among those that were HIV exposed
14.	Riemer [2019] (90)	South Africa (2012 – 2014)	Retrospective cohort (316*:1263) * Does not distinguish between children with and without HIV	**None:** 11% **Unknown:** 10% **Prophylaxis:** 16% **ART**: 62%	Not reported	Mortality	Not specified	Overall mortality**:** aOR=1.39 (95% CI: 0.99-1.97) mortality in ≥1000g (birth weight) infants: aOR=0.87 (95% CI: 0.51-1.48) mortality in <1000g (birth weight) infants: aOR=1.75 (95% CI: 1.13-2.69) mortality (≥8 weeks maternal antenatal prophylaxis/ ART): aOR= 1.45 (95% CI: 0.93-2.25)	Overall mortality**:** Maternal hypertension, antenatal steroids, delivery mode, infant sex, gestation at birth, birth weight Mortality by birth weight: Maternal hypertension, antenatal steroids, infant sex, gestation at birth, birth weight, mode of delivery Mortality by prophylaxis/ART treatment:	Single-centre study – limited generalisability Several confounders not accounted for e.g. SES, substance use Could not separate ARV prophylaxis from ART in analyses Does not distinguish infants who were with and without HIV, among those who were HIV-exposed

No	Author, [year], (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: children HEU vs. HUU point estimate (95%CI)/ proportions¥	Factors adjusted for in point estimates	Study limitations
								mortality (<8 weeks maternal antenatal prophylaxis/ ART): aOR=1.37 (95% CI: 0.79- 2.38) * Didn't distinguish children with and without HIV	Maternal hypertension, antenatal steroids, infant sex, gestation at birth, birth weight, mode of delivery	
15.	Twabi [2020] (91)	Malawi (2010 & 2015 – 16)	Secondary analysis of Malawi Demographic and Health Surveys data (cross sectional) 2010: (316*:2681) 2015: (234*:2456) *Does not distinguish between children with and without HIV	Proportions not reported	Not reported	Perinatal mortality	Up to 12 months	Overall perinatal mortality: 2010: aOR= 1.50 (95% CI: 1.10- 3.10) 2015: aOR=1.00 (0.40-1.60)	Variables included in propensity score model: Age, residence, region, wealth, marital status, ever terminated a pregnancy, anemia, body mass index	Information on deaths collected retrospectively – potential recall bias Cross-sectional data – limited assessment of causal effect of maternal HIV status on infant mortality Potential unmeasured confounding Limited data on ART use Does not distinguish infants who were with and without, among those who were HIV-exposed
16.	Wolter [2023] (92)	South Africa (2016 – 2018)	Cross-sectional (526:723) *47 children with HIV	**Maternal ART during pregnancy:** Children HEU: 98.1% Children with HIV: 92.1%	**Exclusive breastfeeding:** 53.4% **Mixed feeding:** 18.1% **Formula feeding:** 25.2%	In-hospital mortality	<12 months	**In-hospital mortality:** Children HEU vs. HUU: aOR=0.80 (95% CI: 0.31-2.09) Children with HIV vs. HUU: aOR=4.79 (95% CI: 1.49-15.37)	Mother/caregiver educational level, child age group, malnutrition, feeding type, vaccination	Self report classification of mothers living with HIV Out-of-hospital deaths not reported No data on important maternal characteristics e.g. maternal age – potential residual confounding Small sample size

No	Author, [year], (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: children HEU vs. HUU point estimate (95%CI)/ proportions¥	Factors adjusted for in point estimates	Study limitations
Studies reporting on infectious disease morbidity										
17.	Anderson [2021] (96)	South Africa (2017 – 2019)	Prospective cohort study (463:466)	**Maternal ART at conception:** 53% **Maternal ART start during pregnancy**: 27% **Maternal ART restart during pregnancy:** 19%	**Received any breastmilk:** 99%	Hospitalisation (all-cause, infection-related)	28 days	**All-cause admission:** aOR=0.65 (95% CI: 0.43-0.97) **Infection-related admission:** aOR=0.65 (95% CI: 0.33-1.25)	Maternal age, maternal education, housing, twin status	Potential missed hospitalisation/deaths that occurred in other provinces Generalisability of findings is limited Didn't examine exclusiveness of breastfeeding Study wasn't originally powered to compare hospitalisation over 28 days
18.	Anderson [2021] (24)	South Africa (2017 – 2019)	Prospective cohort (455:458)	**Maternal ART at conception:** 53% **Maternal ART start during pregnancy**: 27% **Maternal ART restart during pregnancy:** 19%	**Median duration of breastfeeding (months):** median (IQR) Children HEU**:** 3.0 (1.0-6.2) HUU: 6.1 (2.4-12.0)	Hospitalisation (all-cause, infection-related)	29 days – 1 year	**Infection-related hospitalisation:** aIRR=2.84 (95% CI: 1.49-5.39)	Maternal education, Maternal age, housing, child sex, vaccination status	Potential for unmeasured confounding Potential missed hospitalisation/deaths that occurred in other provinces Potential HIV exposure status misclassification
19.	Goetghebuer [2019] (97)	Belgium (2010 – 2013)	Prospective cohort (132:123)	**Maternal ART initiation**: Before pregnancy: 61% During pregnancy:39%	**Breastfeeding:** Children HEU: none HUU: 95% for median of 6 months	Hospitalisation for infection for >24 hours	Up to 12 months	**Infection-related hospitalisations:** Overall: aHR=2.33 (95% CI: 1.10-4.97) Initiated ART before pregnancy: aHR=1.42 (95% CI: 0.58, 3.48) Initiated ART during pregnancy: aHR=3.84 (95% CI: 1.69-8.71)	**All estimates:** Birth weight, gestational age, literacy, maternal education, maternal African origin, maternal age, primiparity	Adjusted for birth weight and gestational age Single site study – limits generalisability Small sample size

No	Author, [year], (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: children HEU vs. HUU point estimate (95%CI)/ proportions¥	Factors adjusted for in point estimates	Study limitations
20	Labuda [2020] (98)	United States (2006-2017)	Retrospective cohort (2404: 3,605,864)	**Maternal ART during pregnancy:** cART with ≥3 classes: 7% Integrase inhibitor based cART: 8% Nonnucleoside reverse transcriptase inhibitor based cART: 9% Protease inhibitor based cART: 65%	None	Hospitalisation (all-cause, infection-related)	Up to 2 years	**Infection-related hospitalisations:** First admission: uIRR=2.31 (95% CI: 2.02-2.64) Total admissions: uIRR=2.17 (95% CI: 1.92-2.44)	None	Data for children HEU and HUU collected using 2 different sources No data on confounders in HUU children
21.	S. Le Roux [2020] (17)	South Africa (2013 – 2017)	Prospective cohort (459:410)	Maternal ART started at first ANC visit **Median duration of ART use during pregnancy (weeks):** 17 (95% CI: 11-22)	**Ever exclusively breastfeed:** Children HEU: 91% HUU: 81% **Duration of any breastfeeding (months):** Children HEU: 4 (95% CI: 1-12) HUU: 9 (95% CI: 3-12)	Hospitalisation (all-cause, infection-related) Infectious illness: diarrhoea, presumed LRTI	Up to 12 months	**Infection-related hospitalisations:** Overall: uIRR=1.40 (95% CI: 0.97-2.02) 8 days – 3 months: uIRR=3.50 (1.68-7.30) Mothers who started ART <24 weeks gestation, had CD4 count >350 cells/µL, & HIV viral load < 4.0 log_{10} copies/mL: aIRR=1.28 (95% CI: 0.27-6.05) Mothers who started ART ≥24 weeks gestation, had CD4 count ≤350 cells/µL, & HIV viral load ≥ 4.0 log_{10} copies/mL: aIRR=5.01 (95% CI: 1.50-16.71)	**Infection-related hospitalisations:** Both adjusted estimates: Access to running water, a flushing toilet, preterm birth, maternal postpartum depression, low birth weight, season at birth, breastfeeding practice, vaccination completion **Infectious illness:** Both adjusted estimates: Maternal education, access to running water, a flushing toilet, smoking, intimate partner violence, preterm birth, low birth weight, season at birth, breastfeeding practice, vaccination completion	Only included women 18 years and older – potential bias/ reduced generalisability Potential measurement error of infectious illness due to recall bias Transfers/admissions in other provinces not accounted for – underestimates hospital admissions Single facility – reduced generalisability Not generalisable to women initiating ART pre pregnancy Small sample size

No	Author, [year], (citation)	Country (Study period)	Study design (sample size, children HEU:HUU)	Maternal ART/ARV prophylaxis use	Breastfeeding characteristics	Outcomes	Follow-up	Findings: children HEU vs. HUU point estimate (95%CI)/ proportions[¥]	Factors adjusted for in point estimates	Study limitations
								Infectious illness: <u>Birth – 6 months:</u> <u>LRTI:</u> aPR=4.69 (95% CI: 2.40-9.17) <u>Diarrhoeal disease:</u> aPR=2.93 (95% CI: 1.70-5.07)		
22.	Tchakoute [2018] (93)	South Africa, Nigeria (2013 – 2017)	Multicentre longitudinal (537:212)	**Maternal:** Pregnant women living with HIV received ART according to country's guidelines (99%)	**Exclusive breastfeeding:** Children HEU: 93% HUU: 99%	Infectious morbidity: LRTI, diarrhoea, sepsis, meningitis	Up to 12 months	**All infectious events:** <u>Overall</u>: aHR=1.01 (95% CI: 0.78-1.32) <u>Formula feeding vs. exclusive breastfeeding</u> aHR=1.64 (95% CI: 1.04-2.63) <u>non breastfed vs. mixed fed</u> aHR=1.42 (95% CI: 1.00-2.08) <u>Exclusively breastfed 6 months vs. Non-exclusively breastfed</u> aHR=0.77 (95% CI: 0.56-1.06)	<u>All point estimates:</u> Maternal education level and occupation, maternal CD4 count at delivery, infant birth weight, gestational age at birth, feeding practice, clinical site, and Cotrimoxazole use	Uncertainty in HIV exposure and infection status of infants Inclusion criteria: Infants >2.4kg, uncomplicated pregnancy and delivery, >36 weeks gestation a birth – representative of a healthier population. Possible underestimation of outcomes Potential misclassification bias Nigerian infants mostly exclusively breastfed – generalisability limited to South Africa
23.	Wedderburn (2024) (23)	South Africa (2012 – 2015)	Prospective cohort (247:889)	**Maternal ART at conception:** 40% **Maternal ART during pregnancy:** 60%	**Ever breastfed:** Children HEU: 46% HUU: 95%	Hospitalisation (all-cause, infection related)	Up to 24 months	**All-cause hospitalisation:** aHR=1.54 (95% CI: 1.19-2.00) **Hospitalisation for gastroenteritis:** uOR=2.35 (95% CI:1.36-4.04)	Maternal education, maternal smoking, household income, maternal age	Potential missing hospitalisations Low breastfeeding rates Findings not generalisable to settings with high child HIV prevalence

[¥] All ART and Prophylaxis exposure refers to medication given to the mother.

Abbreviations – a: adjusted; ANC: antenatal care; ART: antiretroviral therapy; ARV: antiretroviral; c: combination; HEU: children HIV-exposed uninfected; HUU: children HIV-unexposed uninfected; CI: confidence interval; HIV: Human immunodeficiency virus; HR: hazard ratio; IRR: incidence rate ratio; LRTI: lower respiratory tract infection; kg: kilogram; PR: prevalence ratio; OR: Odds Ratio; u: unadjusted

1.2.6. Risk factors for morbidity and mortality in children HEU vs. HUU

In this section I will give a brief overview of the risk factors thought to play a role in increased morbidity and mortality in children HEU relative to HUU.

There are risk factors that are both universal to all children and risk factors specific to children HEU which may increase their risk of infectious morbidity and mortality (9). These exposures have been reviewed in detail by Slogrove (74). Universal risk factors include: poverty/ SES, being born preterm/ underweight/ SGA, poor nutrition, exposure to infectious pathogens, poor maternal health, suboptimal breastfeeding, all of which are thought to occur more frequently in children HEU relative to HUU. There are however additional risk factors that are mostly unique to children HEU: an HIV affected *in utero* environment, antiretroviral drug exposure and compromised maternal immunity (74). Given that these factors have been reviewed in detail by Slogrove and a detailed discussion on each of these factors is beyond the scope of this literature review, I will provide an overview of the most commonly reported risk factors for infectious morbidity and mortality among children HEU: immunological abnormalities, breastfeeding, maternal ART use, and maternal health (74).

1.2.6.1. Immunological abnormalities

Evans *et al.* have proposed a conceptual framework explaining the susceptibility of children who are HEU to infection (15). A large part of the framework points to immunological abnormalities among children HEU as a result of *in utero* and postnatal exposures leading to chronic inflammation and immune activation. The immunological effects in children are broad, spanning both the adaptive and innate immunity (100). In one aspect, direct HIV exposure and/or the diminished transfer of antibodies across the placenta are thought to be linked to immunodeficiency. Exposure to ART and maternal co-infections have also been seen to result in increased activation of the infant immune system (15). Due to poor health, co-infections are more common in women living with HIV vs. those who are living without HIV and could lead to increased incidence of co-infections in infants, e.g. cytomegalovirus, which in turn can cause immune activation and chronic inflammation (15). Immune activation and chronic inflammation feed into immunodeficiency which then aids the increased frequency

and severity of infections. Although the common causes of infectious morbidity are the same in children who are HEU and HUU, it is possible that the increased frequency of hospitalisation and mortality among children HEU is as a result of the greater severity of the childhood infections amongst this population (9). It is also thought that the increased risk of immunological activation experienced by children HEU could be compounded by factors such as poor maternal health (12).

Vaccination has been shown to reduce morbidity and mortality due to respiratory illness or diarrhoea among children HEU (101). Moreover, children HEU and HUU have been reported to have similar rates of seroprotection against vaccine preventable infectious illnesses (102). It has therefore been suggested that increased infection-related disease in children HEU is due to cellular, as opposed to humoral immune defects (103). The recommended vaccination schedule in SA and the WC, for children up to age 18 months, is described in Table 1.8. The major changes to the vaccination schedule during the study period were a) the introduction of the Pneumococcal and Rotavirus vaccines into the schedule in 2009, b) the replacement of Pneumococcal 7-valent conjugate vaccine with the Pneumococcal 13-valent conjugate vaccine in 2011, and c) the replacement of the pentavalent Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and Haemophilus influenza type b (DTaP-IPV/Hib) and Hepatitis B (Hep B) vaccines with a Hexavalent vaccine (DTaP-IPV-Hib-Hep B) (104,105). According to the *District Health Barometer* (an annually published report giving an overview of public healthcare service delivery in SA), the vaccination coverage, under age 12 months, in the WC has bidirectionally changed over time. The vaccination coverage under age 12 months was estimated to be 85% in the WC in 2010/11 and reached a peak of 87% in 2014/2015 before decreasing to 77% in 2016/17 (106,107). This decrease was due to a shortage in the Hexavalent and BCG vaccines (108). In 2019/2020, the vaccination coverage in the WC had increased to an estimated 85% (107). Vaccination coverage is not disaggregated or reported by child HIV exposure status. Given the immunodeficiencies experienced by children HEU and the potential of vaccinations to induce seroprotection against infectious diseases, it is essential that vaccination coverage is improved to reduce the risk of infectious disease morbidity and mortality amongst children HEU.

Table 1.8: Expanded Programme on Immunisation schedule, up to age 18 months, in South Africa and the Westen Cape during the study period (2008 - 2021)

Child age	Vaccine
Birth	BCG
	OPV 0
6 weeks	OPV 1
	RV 1[¥]
	DTaP-IPV/Hib 1[†]
	Hep B 1[†]
	PCV_7 1[¥]
10 weeks	DTaP-IPV/Hib 2[†]
	Hep B 2[†]
14 weeks	RV 2[¥]
	DTaP-IPV/Hib 3[†]
	Hep B 3[†]
	PCV_7 2[¥]
9 months	Measles 1[‡]
	PCV_7 3[¥]
18 months	DTaP-IPV/Hib 4[†]
	Measles 2[‡]

[¥] RV and PCV vaccines were introduced into the Expanded Programme on Immunisation in 2009 (104). In 2011, PCV7 was replaced with PCV13.

[†] In 2015 the pentavalent DTaP-IPV/Hib and Hep B vaccines were replaced with a hexavalent vaccine (DTaP-IPV-Hib-Hep B) (105).

[‡] In 2015 guidelines changed to recommend that measles 1 and 2 are given at 6 and 12 months instead of 9 and 18 months (105).

Abbreviations – BCG: Bacillus Calmette Guerin; DTaP-IPV/Hib: Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and Haemophilus influenza type b; Hep B: Hepatitis B; PCV: Pneumococcal Conjugated Vaccine; OPV: Oral Polio Vaccine; RV: Rotavirus vaccine

1.2.6.2. Maternal health

In the era of poor access to antiretrovirals, maternal mortality was estimated to be substantially higher among women living with HIV in comparison to those who were living without HIV (109). Moreover, evidence suggests that the risk of mortality among infants born to women living with HIV, irrespective of infant HIV infection status, is greater for infants whose mothers have died relative to those whose mothers are still alive (110). Even in the absence of maternal death, the consequences of having a mother living with HIV can be far-reaching through poor maternal health. This can directly affect household income earning abilities which will in turn impact food security (i.e. child nutrition) and access to healthcare. General care of children HEU may also be neglected (12). Furthermore, food insecurity may negatively influence adherence to ART and other HIV-related healthcare recommendations (111). Although, to my knowledge, a mediation analysis has not yet been conducted, it has been hypothesised that maternal health may mediate the pathway between infant HIV exposure and infectious disease outcomes (14). Moreover, studies defining maternal health using maternal HIV clinical stage, CD4 count or haemoglobin levels found that children HEU and whose mothers had poor health were more likely to die than a) children HEU and whose mothers had better health or b) children HUU (17,68). Le Roux *et al.* (described in section 1.2.5.2) observed that infectious disease hospitalisation rates were similar (although the estimate of the association was imprecise) between children HEU and HUU when mothers of the former initiated ART early and were at an early disease stage of HIV, but that the relative risk was highest when mothers initiated ART late and had advanced HIV disease (17). Beyond the social effects of poor maternal health on health outcomes of children HEU, it is thought that fetal immune activation, due to direct exposure to high viral loads *in utero*, may negatively impact infant health outcomes (15). This highlights the importance of early initiation of ART to not only reduce direct physiological exposure to maternal HIV, but also to limit the broader indirect effects.

1.2.6.3. Maternal antiretroviral prophylaxis and treatment

Benefits of antiretroviral use during pregnancy include improved maternal health and reduced risk of vertical HIV transmission (112,113). In turn, many of the effects of poor maternal health discussed above may be ameliorated. However, the potential adverse health

outcomes associated with maternal antiretroviral use cannot be overlooked. Several studies have suggested increased risk of preterm delivery, infants being SGA, and LBW in women living with HIV receiving ART during pregnancy compared to mothers living without HIV, although results have been inconsistent (114,115). Furthermore, the increased risk of adverse health outcomes may differ by timing of ART start and ART regimen (116–118). A 2017 meta-analysis reported that women living with HIV who initiated ART before conception were more likely to experience very preterm delivery (birth <34 weeks gestation), preterm delivery and LBW as opposed to those who initiated ART after conception (118). Moreover, the risk of morbidity and mortality is higher among infants born preterm (119). Slogrove *et al.,* using WCPHDC data, reported that mothers on any second or higher line of ART(vs. first line ART) or protease inhibitors (vs. non protease inhibitors) were at higher risk of children being born low birth weight (116). Another WC study found maternal protease inhibitor use (vs. non-nucleoside reverse transcriptase inhibitors) to be associated with preterm delivery (96). Although the adverse birth outcomes associated with different ART regimens have been well researched, how different regimens are associated with outcomes such as infectious disease admissions have not. Another consideration is that sub-optimal maternal ART adherence could contribute towards adverse birth outcomes and infectious diseases. Mothers on second line ART may be less likely to be adherent to ART, so adverse birth outcomes may be a combination of the antiretrovirals themselves and characteristics of the moms (e.g. adherence to ART). Differences in haematological parameters have also been observed among children HEU and whose mothers received antiretrovirals (120,121). Although increased anaemia has been observed to be a risk factor for infectious disease in infants, it has not been determined whether this increased risk is present when comparing children HEU to those HUU (122,123).

Given that there is now universal access to lifelong ART for all people living with HIV there will be more children exposed to antiretrovirals from conception, therefore risk differences between children HEU and HUU could be different from the pre-Universal ART era and it is important to better understand the role of ART in the infectious disease related health outcomes of children who are HEU.

1.2.6.4. Breastfeeding

As described in section 1.2.1, breastfeeding plays an important role in general child development, health and survival (19,20,36). Studies among children HEU have reported a lack of breastfeeding/early breastfeeding cessation as a risk factor for poor health outcomes (70,72,124). An overview of these studies was provided by Evans *et al.* (12). Results of a Ugandan study that were in agreement with this, furthermore saw that the association between HIV exposure status and morbidity was substantially reduced when comparing breastfed children who were HEU to HUU, highlighting that lack of breastfeeding may be partially accountable for the excess risk of poor outcomes among children who are HEU (69). In addition, a mediation analysis study in Botswana estimated that not breastfeeding mediated 47% of the association between HIV exposure status and pneumonia-related mortality (14).

A study among breastfeeding women in Botswana observed that even though mortality was higher among breastfeeding children HEU vs. HUU, the immunological profiles of the breastmilk were comparable among women living with HIV and women who were living without HIV, suggesting that the excess mortality was unlikely due to immunological deficiencies in breastmilk (70). Studies have, however, reported potential differences in human milk oligosaccharides in mothers with HIV (125,126). Changes in human milk oligosaccharides could affect the microbiome of children HEU, which may, in turn, lead to suboptimal health outcomes compared to breastfed HUU children.

The Le Roux *et al.* study (described in section 1.2.5.2) found that with optimal breastfeeding (initiated 1 hr after birth and exclusive up to 3 months of age) and timely vaccination the infection incidence rates among children HEU approximated those of children HUU (although the estimate was imprecise – due to small sample size) (17). The excess risk of infectious disease was substantially higher among children HEU when they were not optimally breastfed. The study suggested that for infectious risks among children HEU to approximate those among children HUU they need to be optimally breastfed and timeously vaccinated, in conjunction with mothers being at a less advanced stage of HIV and initiating ART early in pregnancy. More recent studies have also found breastfeeding to be protective against infectious disease admissions (23,24).

1.2.6.5. Other factors

Other factors that have been observed to be associated with increased morbidity and mortality among children HEU include: smoking during pregnancy (123), infant anaemia (123), intrapartum antibiotic treatment (123), country of residence (123), male gender (127), marital status (15), household income/poverty (15,74), maternal age (although evidence is conflicting) (127,128), poor/suboptimal child nutrition and growth (74), infectious pathogen exposure (74), suboptimal child healthcare seeking behaviour (129), and HIV altered *in-utero* environment (74).

1.2.6.6. Summary

The network of factors involved in determining morbidity and mortality among children HEU is very complex. Universal risk factors mean that both children HEU and HUU are at risk of infectious disease (9), however, additional factors potentially occurring more frequently in children HEU may contribute to an excess risk in morbidity and mortality. It has been hypothesised that factors such as maternal health and maternal antiretroviral exposure, and breastfeeding may mediate the association between maternal HIV status and infectious disease outcomes (14). Given the complexity of the network of factors associated with poor health outcomes among children HEU it is difficult to establish whether a) the excess risk of infectious diseases that has been observed in many studies is due to biological differences between children who are HEU and HUU or b) maternal HIV status is acting as a proxy for the multiple deprivation experienced by children HEU. The factors that are likely to increase a girl/woman's vulnerability to acquiring HIV and/or becoming pregnant (e.g. SES, substance abuse, intimate partner violence, maternal education) are likely to also be risk factors for poor infant health status, irrespective of any direct impact of HIV on the mother or child. While it would be extremely valuable to disentangle these effects, to improve child health outcomes, it may be equally useful to determine the high vs. low risk groups among children who are HEU, and the respective factors associated with each, to be able to explore ways in which increased risk can be mitigated through targeted interventions.

1.2.7. Challenges in this field of research

As highlighted in previous reviews, studies that have been conducted in the health outcomes field of research among children who are HEU vs. HUU are highly heterogenous, particularly when it comes to maternal ART use, infant feeding, the way in which potential confounding factors have been controlled for, and which confounding variables have been controlled for (11,67). Most studies were conducted during a period in which access to maternal ART was limited and breastfeeding strategies for pregnant women living with HIV varied. Therefore, ART use and infant feeding differed within and between studies. Consequently, these study results may not be generalisable to today's Universal maternal ART and breastfeeding practices across SSA (11,67). Given the benefits of ART in improving maternal health and breastfeeding in improving infant health, it is thought that current practices may mitigate part or all excess risk of infectious disease among children HEU (11).

A particular challenge in past studies was whether an appropriate group of children HUU was included to compare to the HEU study group (or alternatively whether adequate statistical adjustment was made for important factors that differ between them). This is important to account for socio-economic and psychosocial factors that are often associated with maternal HIV, not easily measurable, and likely confounders (11). Moreover, studies were often not designed to primarily compare outcomes of children HEU vs. HUU, but rather formed secondary data analyses from intervention trials. This limits generalisability of study results as participants may have received superior medical care linked to trial participation (11). In addition, secondary data analyses were not able to control for confounders if they were unmeasured in the primary study (68). To date, sample sizes of studies comparing health outcomes in children HEU vs. HUU have been relatively small (10,69,70,73,75,76,97). This limits the statistical power of studies to observe true differences between groups. Small sample sizes may also limit the ability to conduct more complex statistical analyses (130). Ultimately, larger sample sizes are necessary to produce robust results (131). Another factor limiting the generalisability of study results is the fact that study data has often been collected at a single health facility. Given that the effects of maternal HIV on infectious disease outcomes may be context-specific, study estimates may not be externally valid to larger regions within a country.

Classification of child HIV exposure and infection status is complex and the uncertainty surrounding this has often not been acknowledged in studies. Regular repeat HIV testing of mothers and infants/children is necessary to accurately classify children according to exposure and infection status (15). In the absence of repeat testing, especially in settings of high HIV incidence, mothers who seroconvert may not be identified and hence child exposure status will be misclassified. Given that breastfed children are at risk of vertical HIV transmission, particularly in the absence of maternal antiretrovirals, without regular testing some children living with HIV may have been misclassified as children who are HEU, which could inflate outcome estimates. The same applies to antiretroviral exposure classification; antiretroviral exposure can differ by sources (i.e. maternal ART, maternal pre-exposure prophylaxis (PrEP) or infant antiretroviral prophylaxis), type of antiretroviral drug taken, and timing of exposure to antiretrovirals (130). These factors are seldom collectively considered when classifying antiretroviral exposure in studies. Ultimately, standardised exposure definitions, taking into account uncertainties surrounding classification, are required to accurately assess health outcome disparities between children who are HEU and HUU (132).

Another limitation that has been noted in studies comparing health outcomes in children who are HEU relative to HUU is bias due to the selection of study participants. A study assessing the effects of breastfeeding on the association between maternal HIV and infant infectious morbidity selected a cohort that was naturally at low risk for poor health outcomes (93,94). Another study only assessed health outcomes in children surviving to 20 months of age (73). Given that children are likely to experience poor outcomes in their first year of life a discrepancy between children HEU and HUU among those surviving to 20 months is less likely to be observed. Substantial loss to follow-up in studies is also a concern with regards to bias (73). There is also a lack of acknowledgement in many studies of potential bias due to only including liveborn pregnancy outcomes. Evidence suggests that there may be an increased rate of miscarriages and stillbirths among pregnant women living with HIV in both the pre-antiretroviral and antiretroviral era (133,134); thus liveborn infants who are HIV-exposed may have characteristics better enabling them to survive. This could lead to underestimation of the relationship between HIV exposure and poor health outcomes.

Information bias has also been a potential limiting factor in some previous studies. Several studies have had to rely on maternal recall of infectious disease events which could lead to measurement error in study estimates due to recall bias (10,11,17,73).

As discussed above, the network of factors which influence morbidity and mortality is very complex and consequently it has been difficult to separate the biological effects of HIV and antiretroviral exposure on infants from the effects of multiple deprivation experienced by infants born to women living with HIV. Several studies (described in sections 1.2.3 and 1.2.4) did not adjust for confounding factors. Factors that should be adjusted for include maternal age and SES. Other studies have adjusted for these factors but also for others including maternal health and adverse birth outcomes (LBW and preterm birth), on the basis of them confounding the HIV exposure – infectious outcomes relationship (17,76,93). However, these factors may be on the pathway between exposure and outcome (for adverse birth outcomes this would depend on the timing of antiretroviral exposure) and if controlled for will remove the potential important (and of interest) indirect effects of the mediator (135).

In all, the literature has highlighted the need for future research. Well-designed prospective longitudinal cohort studies with a sample that a) is sufficiently powered to assess morbidity and mortality pathways in children who are HEU vs. HUU (130,136), b) representative of multiple socio-economic contexts, c) includes a comparable group of children who are HUU, and d) is able to adjust for key likely confounders, are required to assess the effect of maternal HIV exposure on infectious disease outcomes among children under current policy and in high HIV prevalence settings. These studies should utilise data collected in the current, Universal ART and exclusive breastfeeding, era (including data on health outcomes of children who are HEU and were conceived on ART). There is also a need for studies in which HIV and ART exposure status is well defined, taking associated uncertainties into account. Studies should also carefully consider the likely causal pathways between infant HIV exposure and infectious outcomes so as to not control for potential mediating factors (unless estimating the direct effect of the exposure on the outcome). Furthermore, the requirement for routine-care maternal and child linked health data platforms, which could be used to answer important child health related research questions and facilitate future evidence informed targeted interventions and policy changes, has been highlighted (3,130).

1.3. Aims and objectives

1.3.1. Aims

Among children born in the WC during the years 2008-2018, this research aimed first to systematically classify HIV exposure status. Using these classifications, this research subsequently characterised the HIV-related characteristics of children and their mothers and how they changed in the population over calendar time. Finally, outcomes of infectious disease morbidity and healthcare utilisation were compared by child HIV exposure classification.

1.3.2. Research Objectives

1. Assess the retrospective applicability of a simplified version of The DECIPHER (Data Evaluation and Collaborative Initiation for Paediatric HIV Education and Research (CIPHER) Preparation for an HIV Exposed Uninfected Child CohoRt) project's (137) standardised HIV exposure and infection status definitions to routine longitudinal mother and child healthcare data in the Western Cape.

2. Classify *in utero* child HIV exposure and HIV infection status using simplified DECIPHER definitions and assess how the certainty of these classifications change over time.

3. Describe, at a provincial-level, the temporal changes in HIV-related characteristics (i.e. child HIV infection, child HIV exposure, child exposure to maternal ART, timing of exposure to maternal ART, maternal CD4 count, and maternal viral load) of children aged ≤3 years hospitalised with infectious diseases[b] from 2008 to 2021.

4. Describe the characteristics, causes, rates of, and factors associated with infectious disease hospital admissions in children aged ≤3 years (not known to have HIV) born in the WC between 2013 and 2018 and determine whether these differ by HIV and ART exposure status.

[b] The infectious disease categories considered in analyses throughout this thesis were lower respiratory tract infections, diarrhoea, meningitis, and tuberculous meningitis

5. Determine whether healthcare utilisation up to 18 months of age for well-child visits in a WC provincial cohort of children (not known to have HIV) born between 2013 and 2018 differs by maternal HIV status and engagement in the HIV VTP services.

CHAPTER 2. DATA MANAGEMENT AND STUDY SOURCES

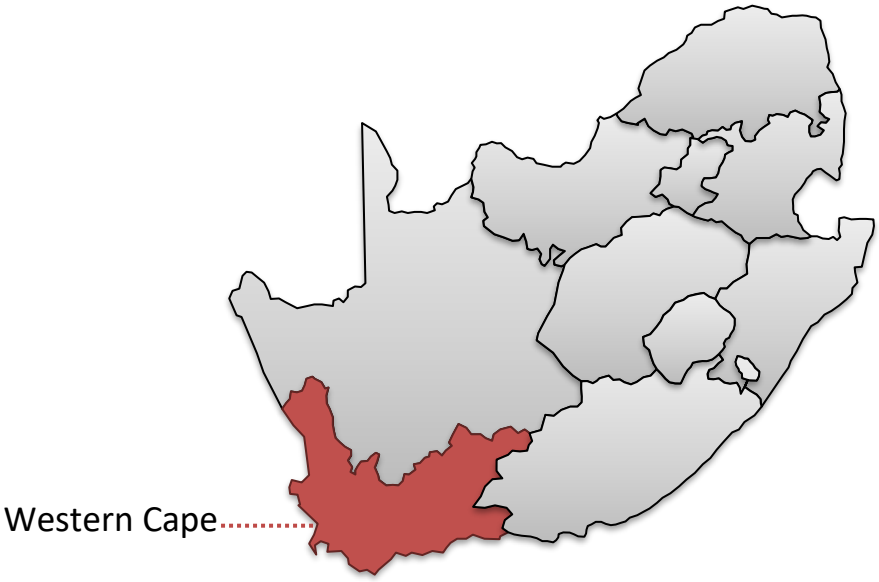
2.1. Chapter overview

This chapter describes the data source, population setting, study participants, data management and key variables used throughout subsequent analyses chapters. Each analysis chapter (Chapters 3 – 6) will provide further detail on respective procedures and measurements (including the defining of exposures and outcomes where applicable), and statistical analyses conducted.

2.2. Population setting

The WC, one of SA's nine provinces, has an estimated population size of 7.4 million individuals (138). The province is divided into six districts, namely: City of Cape Town (i.e. Cape Metropolitan/Cape Metro), Cape Winelands, Central Karoo, Garden Route, Overberg, and West Coast (Figure 2.1). Table 2.1 summarises the socio-economic profiles of the six districts in the WC (139–144). The City of Cape Town is the most populous district with ~4.7 million individuals. In 2020, the province was reported to have substantial income inequality (Gini-coefficient = 0.6) (Gini-coefficient is a statistical measure of the income distribution (inequality) within a population with 0 representing no inequality and 1 representing complete inequality (145)) and an unemployment rate of ~23% (146). In 2021/2022, the unemployment rate was highest in the City of Cape Town at 29% (Table 2.1). In 2019, pre COVID-19, 23% of households in Cape Town earned less than R3500 (~£147) per month, which is an indicator of household poverty, and 20% of houses were informal dwelling types (147). Informal houses are most often built of corrugated iron, hardboard or plastic sheets, with three to four houses sharing a single toilet (74).

A. Map of South Africa



B. Map of Western Cape

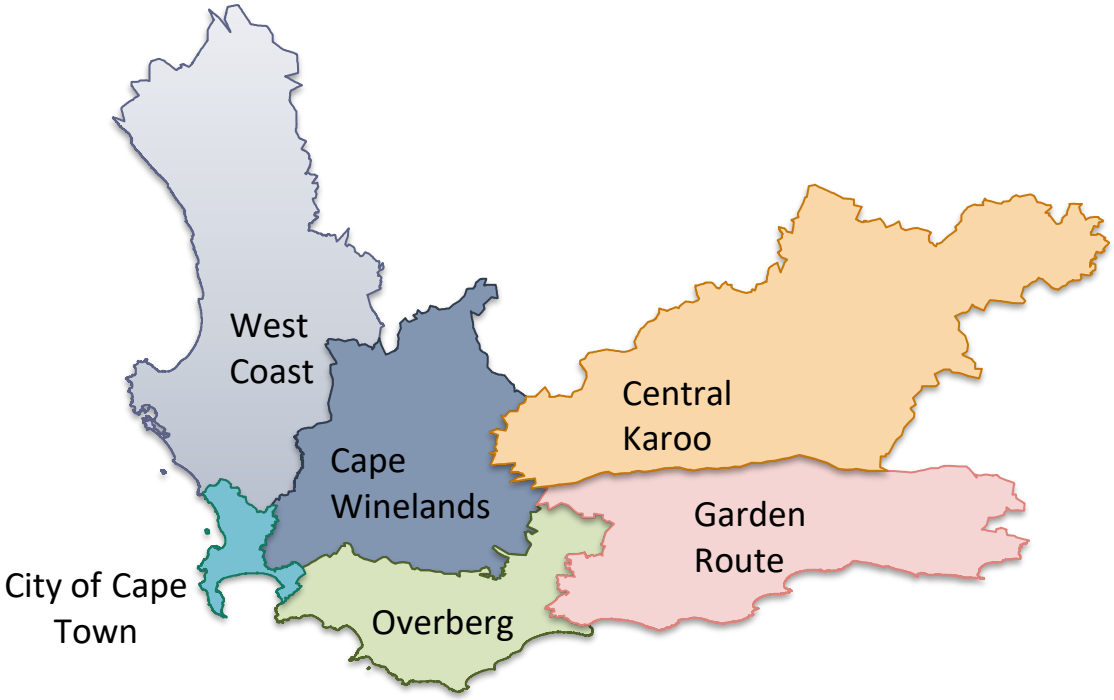


Figure 2.1: Map of (A) South Africa - highlighting the Western Cape and (B) Map of the Western Cape – highlighting its six districts.

**Maps were generated using templates from http://yourfreetemplates.com*

An estimated three quarters of the population in the WC, including most people with HIV, utilise public-sector health services, with high-income groups mainly using private-sector facilities (63,148). The public sector comprises 272 primary care clinics and 52 hospitals managed by the Provincial Department of Health, with an additional 52 clinics being managed by the City of Cape Town municipality (148). There are an estimated 15 million patient-contacts with these facilities annually, with ~110,000 pregnancies and ~90,000 deliveries being recorded annually within the WCPHDC (described in section 2.3). Primary healthcare facilities provide antenatal care (ANC) and uncomplicated vaginal delivery services. Public sector hospitals include District, Regional, Tertiary and Central hospitals (149). District hospitals are the usual entry point into the hospital system, with complicated cases being referred to Regional, Tertiary, or Central hospitals for specialist care (150). In the late 1990s and early 2000s, ill children, particularly children with HIV (CWH) or children HIV-exposed, were admitted to Tertiary/Central hospitals. However, over time there have been changes to paediatric healthcare organisation in SA, with increased district hospital capacity and less dependence on tertiary hospitals (151,152).

According to the 2022 Antenatal HIV survey, antenatal HIV prevalence in the WC, among women 15 to 49 years of age, was estimated to be 16%, a 1.5% decrease from 2019 and lower than the national prevalence of 28% (58). HIV prevalence was estimated to be highest in the Overberg (20%) and City of Cape Town (20%) districts. The survey estimated that 80% of women living with HIV were estimated to have HIV status knowledge prior to pregnancy, of which 73% were reported to have initiated ART prior to pregnancy (58). The proportion of pregnant women living with HIV knowing their HIV status prior to pregnancy was the lowest in Overberg (71%) and the highest in the Central Karoo (92%), while ART initiation prior to pregnancy, amongst women who knew their HIV status, ranged from 68% in Cape Town to 82% in Overberg (58). In 2017, provincial vertical HIV transmission was estimated to be 2-3% at 18 months of age (63). In Khayelitsha, the subdistrict in the WC with the highest antenatal HIV prevalence (32%), vertical transmission was reported to be 1.8% at age 12 months in 2017, with 95% of women diagnosed with HIV before delivery having initiated ART (153).

Table 2.1: Summary of the socio-economic profile of the six Western Cape districts in 2021/2022

Characteristic	District					
	City of Cape Town	Cape Winelands	Central Karoo	Garden Route	Overberg	West Coast
Population size estimate: n	4,748,976	968,667	75, 897	632,329	310,253	476,020
GDP per capita: Rands (Pound sterling)	90,050 (~3751)	67,798 (~2,824)	38,059 (~1,585)	69,165 (~2,881)	63,994 (~2,666)	61,352 (~2,556)
Unemployment: %	29	15	23	21	16	16
Learner retention[¥]: %	75	76	62	72	72	75
Access to services						
Water	99	99	99	98	99	99
Electricity	97	96	88	95	95	96
Sanitation	94	97	98	84	98	88
Child malnutrition[†]:	1	2	2	2	2	2
Neonatal mortality rate[‡]:	8	8	8	8	6	8

[¥]Learner retention is the proportion of learners completing the compulsory schooling level (grade 12 in South Africa) through continued participation. Continued participation is defined as the proportion of grade 12 learners who completed grade 10 two years prior to completing grade 12.

[†]n/100,000 children under age 5

[‡]n/1000 live births

Abbreviations – GDP: Gross domestic product

2.3. Study design and data sources

This thesis comprises retrospective, population-based, cohort analyses using digitised routine maternal and infant healthcare data housed within the WCPHDC. The WCPHDC profile has been described in detail elsewhere (148). Briefly, the WCPHDC is a digital health information platform that consolidates multiple sources of individual-level data from provincial public sector health service systems in the Western Cape (WC). Data consolidation is done using a unique patient health identifier which is generated for patients when they first attend healthcare services. This allows the linkage of data on hospital admissions, outpatient visits, laboratory test results and pharmacy records into a single individual-level data repository (Figure 2.2). Data on mothers and their children are also electronically linked.

All available data sources are then used to infer individual encounters with the healthcare services, health conditions (episodes) and subsequent health outcomes. The utilisation of multiple data sources to infer health conditions strengthens the confidence of the inferred condition. Health condition episodes are then stored in either cascades or tables. Cascades are one line per health condition integrated with additional characterising information necessary for patient care (e.g. the maternity cascade will have data pertaining to a single mother-child pair as well as adherence markers for the mother/child if living with HIV). Data tables can have multiple rows per patient with data on just a particular domain (e.g. data pertaining to just births). These cascades and tables form virtual cohorts which are continuously updated. Outputs are then drawn from these databases for dashboards, management reports, viewing tools, and research requests.

Although mother and child data were already linked within the WCPHDC, the data that I required for my analyses were distributed across multiple cascades and tables which I needed to link to form my own dataset. Furthermore, certain markers within the maternity cascade (e.g. child HIV status) were only relevant for that cascade up to child age two years and as I needed data up to age three years, I needed to re-link and redefine these variables.

2.4. Study participants

For Chapters 3 – 7 of this thesis, the overarching inclusion and exclusion criteria that I used to select children into my datasets were as follows: I included children born in a WC public health facility, that reported to the WCPHDC, between 2008 and 2018 – in the earlier years of the period under analysis, not all facilities (particularly those in rural areas) had electronic records (the shift to digitisation has been incremental over time). This has been acknowledged within individual analyses chapters. Only children with a birth outcome classified within the WCPHDC as “live birth”, “early neonatal death” or “late neonatal death” (i.e. live births) were included.

The total number of electronically-recorded live births at a WC public health facility during the maximum study period (2008 and 2018) was N=565,052.

Across all analysis chapters, to accurately classify child HIV infection and *in utero* HIV-exposure, children were excluded if there was missing/inconclusive data on maternal HIV status during pregnancy for any of the following reasons:

1. They could not be linked to their mothers.
2. Their mother had HIV but her HIV first evidence date was more than 10 weeks after child's date of birth, such that it was unclear whether the child was exposed to HIV *in utero*[c].
3. The child or mother had data inconsistencies (e.g., a negative HIV-PCR result after evidence of having HIV), such that it was unclear whether the child or mother were living with HIV.

Additional inclusion and exclusion criteria with respect to children with HIV, birth year, and/or multiple pregnancies were specific to each analysis chapter and are summarised in Table 2.2. In each chapter, a flow chart is presented to show all exclusions from the full N=565,052, including exclusions due to #1-3.

[c] Up to 10 weeks postnatal was used as a reasonable time-period to consider that a child was exposed to HIV *in utero* – as the window period between HIV exposure and a positive HIV (ELISA/rapid) test result is 4 to 12 weeks. Most maternal diagnoses would be made with antibody tests. Ten weeks postnatally was also a consistent age for classifying child birth HIV infection status as guidelines recommended infant HIV-PCR testing at birth and age 10 weeks.

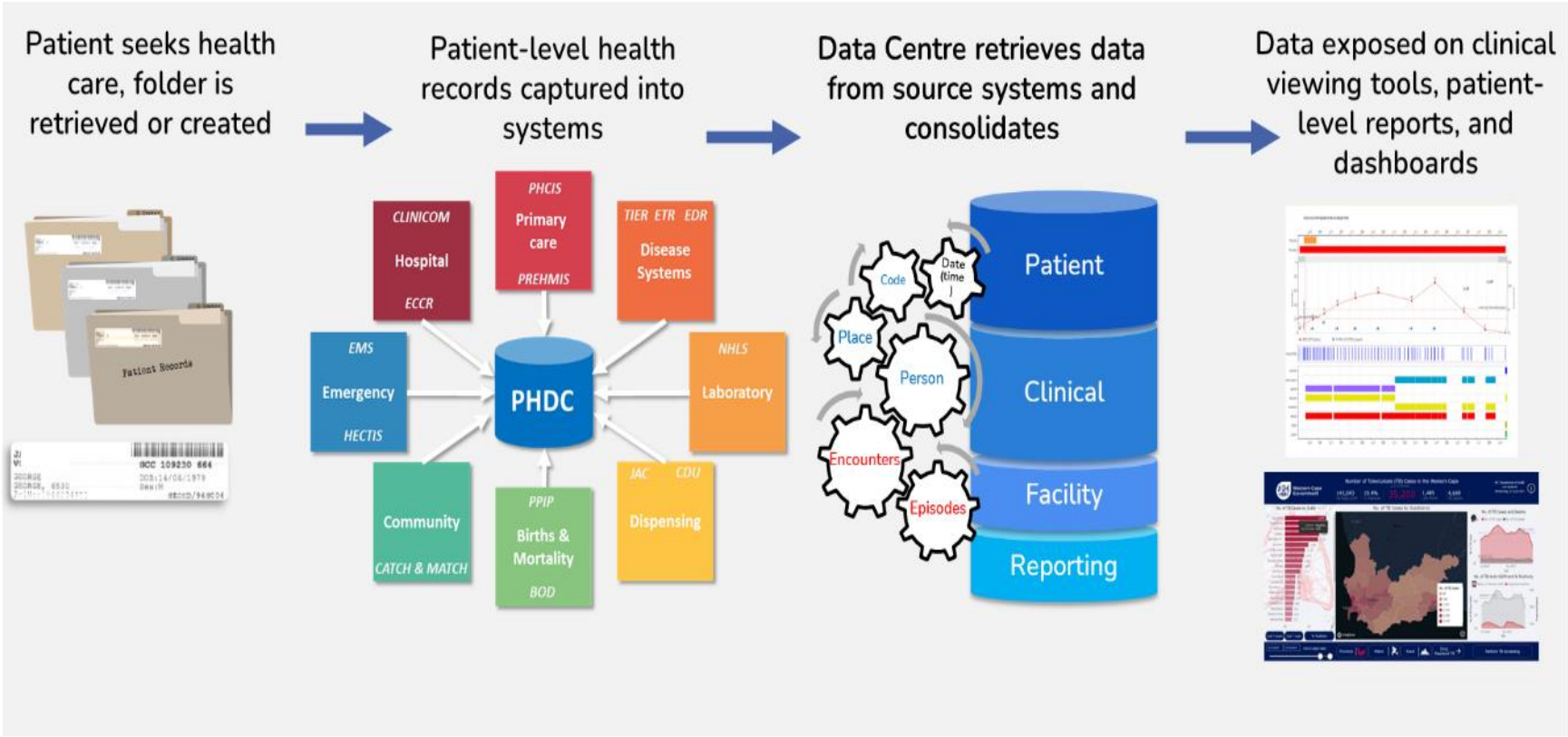


Figure 2.2: The flow of routine healthcare data into and through the Western Cape Provincial Health Data Centre

Abbreviations – BOD: Burden of Disease; CDU: Chronic Dispensing Unit; ECCR: Electronic Continuity of Care Record; EDR: Electronic Drug Resistant Register; EMS: Emergency Medical Services; ETR: Electronic TB Register; HECTIS: health and emergency centre tracking information system; NHLS: National Health Laboratory Services; PHCIS: Primary Healthcare Information System; PPIP: perinatal problem identification system; PREMIS: Patient Record and Health Management Information System; TIER: Three interlinked Electronic Registers. **Figure Source**: Reproduced from Euvrard *et al.* (154) Under a CC BY 4.0 license.

Table 2.2: Inclusion and exclusion criteria specific to each chapter

		Inclusion/exclusion criteria					
Thesis chapter	**Chapter title**	**Year of child birth**	**Children HUU**	**Children HEU**	**Children with HIV**	**Multiple pregnancy**	**Other**
Chapter 3	HIV exposure classification	2008 – 2018	Included	Included	I aimed to exclude children born with HIV (up to age 10 weeks) and to include children with evidence of HIV > age 10 weeks if they were known to not have HIV by age 10 weeks: ▪ Excluded if child HIV first evidence date was ≤ age 10 weeks (couldn't be certain they weren't born with HIV) ▪ Excluded if child HIV first evidence date was > age 10 weeks without a prior HIV negative test result > age 10 weeks or none at all (i.e. they had unknown timing of HIV acquisition) ▪ Included if child had a HIV negative test result > age 10 weeks and had a subsequent HIV first evidence date	All children included	▪ Hospitalised and non-hospitalised children were included
Chapter 4	Change in HIV-related characteristics of children hospitalised with infectious diseases	2008 – 2018	Included	Included	I aimed to include only children whose HIV exposure and infection status was known at the time of admission. Children born with HIV or diagnosed with HIV during the study period were included, but I excluded children who had an unknown timing of HIV acquisition relative to hospital admission: ▪ Excluded if child HIV first evidence date was after hospital discharge with no negative HIV test result between discharge and HIV first evidence date	All children included	▪ Only children who had an infectious disease hospitalisation record between 2008-2021 were included

		Inclusion/exclusion criteria					
Thesis chapter	**Chapter title**	**Year of child birth**	**Children HUU**	**Children HEU**	**Children with HIV**	**Multiple pregnancy**	**Other**
Chapter 5	Infectious-cause hospitalisation in children HEU and children HUU in the Western Cape, South Africa	2013 – 2018[¥]	Included	Included	▪ As for Chapter 3	All children included	▪ Hospitalised and non-hospitalised children were included
Chapter 6	Healthcare utilisation for well-child visits compared by maternal HIV status and engagement in HIV vertical transmission prevention services	2013 – 2018[¥]	Included	Included	▪ As for Chapter 3	1 child of each multiple pregnancy was randomly included[†]	▪ Same cohort of children who were included for Chapter 5 with the additional exclusion of siblings from multiple pregnancies and children whose linkage to their mother or siblings was not robust[‡] ▪ Hospitalised and non-hospitalised children were included

[¥]A shorter date range was more appropriate for Chapters 5 and 6 as they were focused on the Option B+ and Universal ART periods

[†]Children from multiple pregnancies (pregnancies with more than one child) are likely to attend the same well-child visits; one child of each multiple pregnancy was therefore randomly selected and additional children (twins, triplets or quadruplets) excluded from analyses

[‡]Additional data extraction for Chapter 6 was done a year after data extraction for Chapters 3 – 5. There is ongoing improvement of the unique identifiers within the WCPHDC and there were therefore mother-child and sibling linkages from the initial extraction that were no longer considered robust by the WCPHDC in the most recent extraction. Examples of non-robust linkages include: two children with the same unique identifier and different mothers; twins, triplets, or siblings with the same unique identifier; a single child given two unique identifiers

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected; WCPHDC: Western Cape Provincial Health Data Centre

2.5. Data management and extraction

As described in the study design and data source section, the WCPHDC consolidates data from multiple sources into a single platform. Using a unique identifier the WCPHDC are able to link individual-level data across systems (148). Once data are imported into the WCPHDC, it undergoes cleaning, mapping and processing (e.g. weighting of evidences' contribution to conferring health episodes). The processed data are then stored within the Patient and Clinical databases within the WCPHDC. Using the processed data, the WCPHDC infers individual patient health conditions and encounters with health facilities. Health condition data are then integrated with other related characterising data, needed for patient management or research, and/or indicators calculated within the WCPHDC into cascades/tables (e.g. maternity cascade, which includes mother and child data for each pregnancy such as demographics, pregnancy evidence, date of child birth, child sex, birth weight, multiple pregnancy status, parity etc.).

Working closely with a data analyst from the WCPHDC, I undertook a substantial amount of work to manage and extract the data required for the analyses in this thesis. I was responsible for creating the base datasets required for this thesis, utilising the database cascades and tables housed within the WCPHDC. This was an iterative process which involved the following tasks:

- Writing, checking, and correcting the SQL server code required to link and integrate predefined maternal and child health data variables from multiple tables within the WCPHDC. Although some variables were predefined and linked within the WCPHDC (e.g. child date of birth and child HIV evidences), these were stored within different tables/cascades within the data centre (Table 2.3) and needed to be linked using unique maternal and child identifiers to form a base dataset specific to my thesis needs.
- Merging the data from multiple tables using the above mentioned code.
- Defining and creating additional variables required for analyses (e.g. HIV exposure status and certainty thereof – detailed in Chapter 3). More complex variables (not

predefined within the WCPHDC) that I defined using two or more parameters within the WCPHDC were generally defined using the SQL server at the same time as data merging. For example, I defined child HIV exposure and certainty status using a combination of maternal HIV first evidence date, child laboratory test type, date, and result (three different parameters that I used to determine last HIV negative test date) as well as child HIV first evidence date. I used Stata software to define variables that used only a single parameter from the WCPHDC (e.g. the categorisation of child birth weight) after data extraction. Variables that I needed to define are described in section 2.6 and subsequent analyses chapters.

- Performing data quality checks; investigating identified data issues; consulting the data analyst within the WCPHDC regarding data issues; correcting for data issues.
- Data extraction using WCPHDC data extraction protocol.
- Further data management (categorisation of variables as mentioned above and exclusion of participants not meeting inclusion criteria), cleaning (e.g. re-coding of implausible child birth weights as missing; replacing mother and child death dates as missing if they had conflicting evidence against death – described in section 2.6) and data quality checks using Stata. If data errors were identified in Stata (examples are provided below) then all above mentioned steps were repeated.

Carrying out the above tasks:

To start, I was unfamiliar with coding using SQL server and undertook self-learning through online courses to develop these skills. I was also unfamiliar with the back-end of the WCPHDC and underwent initial training of how to access data and join tables etc. I then had regular meetings with a data analyst who would guide me in the direction of which tables to use, explain the parameters within these tables, assist with coding challenges, and guide me on how to do data checks and validation using multiple tables within the WCPHDC. The meetings were based on queries that I had and hence mainly retrospective guidance. I was then responsible for implementing what I had learnt, so that I could progress with the management of my dataset.

I first used the births table within the WCPHDC to identify children whose births were recorded electronically at a public facility within the WC between 01 January 2008 and 31

December 2018. From the births table I obtained the unique identifiers for children and mothers. Using child and mother patient identifiers I was able to join to other cascades and tables within the WCPHDC and link respective child and mother parameters of interest. The cascade/tables that I linked to and parameters that I extracted are listed in Table 2.3. All parameters listed in Table 2.3 were already defined within the WCPHDC. The additional parameters that I defined are described in the variable definitions section below and subsequent analyses chapters.

I ran logic checks on my integrated datasets as a means of data validation – e.g. looking for mothers and children with a negative HIV test result after their HIV first evidence date / child HIV first evidence date before date of birth. I also carried out logic checks for each newly defined variable by comparing the newly defined variable's classifications against the parameters used to define the new variable - i.e. I checked that participants were correctly classified. In the event of logic check discrepancies, I first reviewed my data management code for potential errors. If my code was correct I took a more in-depth look at the data available within the WCPHDC, by comparing data recorded in multiple tables. Additionally, I used Single Patient Viewer (SPV) (in demonstration mode – i.e. participants were deidentified), which is a web-based tool that integrates clinical data for each patient individually (148), to verify data within the WCPHDC (by comparing it to the clinical records within SPV). Data discrepancies/inconsistencies found to be stemming from data processes within the WCPHDC were reported to a data analyst within the WCPHDC. The data analyst would then update and rerun the data processes within the WCPHDC, before I could access the corrected data. If the WCPHDC were able to timeously correct these discrepancies, I would rerun my code to amend my dataset. If discrepancies could not be corrected for, the affected participants were excluded from my dataset. The number of children excluded from the overarching dataset due to such discrepancies (i.e. children or mothers who had data inconsistencies (section 2.4) will be described in each individual analyses chapter).

I used Microsoft SQL Server Management Studio to compile and manage my datasets which were housed within the WCPHDC server. Once datasets were finalised, study participants were allocated study-specific anonymised unique patient identifier and deidentified. Datasets were password-protected and WCPHDC data extraction protocols were followed.

The first dataset that I extracted consisted of all the variables required for Chapters 3 -5 (described in each chapter). For Chapter 6, I required additional data on child health service encounters and dispensing of maternal ART. I only extracted the additional data for participants that were included in Chapter 6. As there is ongoing improvement of the unique identifiers within the WCPHDC, there were mother-child and sibling linkages from the initial data extraction that were no longer considered robust by the WCPHDC in the second extraction. Examples of non-robust linkages include: two children with the same unique identifier and different mothers; twins, triplets, or siblings with the same unique identifier; a single child given two unique identifiers.

Table 2.3: Tables and cascades, from the WCPHDC, and the parameters extracted from each to form a dataset for subsequent analyses

Table/cascade	**Parameters extracted[¥]**
Births table	▪ Child patient identifier ▪ Mother patient identifier ▪ Child date of birth ▪ Child birth outcome (e.g., live birth, early neonatal death) ▪ Child birth weight
Paediatric cascade	▪ Child sex ▪ Birth facility name ▪ Child suburb of residence
Maternity cascade	▪ Child sex ▪ Child date of birth ▪ Birth facility name ▪ Mother date of birth ▪ Mother date of death ▪ Mother pregnancy number (of pregnancies recorded in WCPHDC) ▪ Parity ▪ Mother last HIV negative test date ▪ Single or multiple pregnancy[†]
Laboratory results table (For HIV, viral load and CD4 tests)	▪ Laboratory test type ▪ Laboratory test date ▪ Laboratory test result
Episodes table	▪ Child HIV first evidence date ▪ Child HIV evidence sources[‡] ▪ Mother HIV first evidence date ▪ Mother ART start date ▪ Mother HIV evidence sources [Φ]
Encounters table	▪ Encounter type (e.g. primary healthcare visit) ▪ Encounter date ▪ Encounter facility
HIV ART dispensed table	▪ Date ART was dispensed

Table/cascade	Parameters extracted[¥]
	▪ Date on which dispensed ART would be used up – last ART in hand date
Mortality table	▪ Child date of death ▪ Indicator of conflicting evidence against child date of death ▪ Mother date of death ▪ Indicator of conflicting evidence against mother date of death
Infectious disease hospital admissions table	▪ Date of hospital admission ▪ Date of hospital discharge ▪ Age at hospitalisation ▪ Indicator of death during infectious admission ▪ Indicator of LRTI diagnosis[§] ▪ Indicator of diarrhoea diagnosis ▪ Indicator of TB meningitis diagnosis ▪ Indicator of meningitis diagnosis ▪ Indicator of admission to ICU ▪ Type of admission facility

[¥]Some parameters were repeated in different cascades/tables. These tables were coalesced to ensure the non-missing value (if available) for that parameter was extracted.

[†]Single pregnancy refers to a pregnancy with only one live-born child and multiple pregnancy refers to a pregnancy with more than one live-born child (i.e. twins, triplets, quadruplets)

[‡]Sources used to confirm child HIV first evidence date: a positive HIV polymerase chain reaction (PCR) (HIV-PCR) test result confirmed by a second positive HIV-PCR test; a viral load record; a record of receiving ART for >6 months

[ϕ]Sources used to confirm mother HIV first evidence date: two of any of the following: positive HIV-PCR / HIV ELISA test; HIV viral load / HIV genotypic resistance assay; a CD4 count assay; two antiretrovirals dispensed on the same day; a listed HIV ICD-10 code (B20)

[§]Cause of infectious disease hospital admissions were classified within the WCPHDC using International Classification of Diseases 10th Revision (ICD-10) codes. Further details are given in section 2.6.3.

Abbreviations – ART: antiretroviral therapy; ICU: Intensive care unit; LRTI: lower respiratory tract infection; TB: Tuberculous; WCPHDC: Western Cape Provincial Health Data Centre

2.6. Variable definitions

The definitions of the key variables used throughout chapters 3 – 6 are given below. Exposure and outcome variables and variables specific to individual chapters are described within each chapter.

2.6.1. Maternal variables

- **Age:** Continuous (Chapter 4) and categorical (Chapters 5 and 6) variable. Maternal age at child birth categorised in years as 15-19; 20-39; 40-50. Although there are adolescents aged 10-14 years and women aged >50 years that become pregnant each year, I was unable to verify that these were not data capturing or inference errors and therefore coded their maternal age as missing (N=2,134 (0.4%) of the overarching dataset).
- **Parity:** Categorical variable. This is recorded during current pregnancy and is based on digital evidence of prior pregnancies in the WC only. Older mothers who had pregnancies before digitisation and mothers who had pregnancies in other provinces are therefore less likely to have parity accurately recorded. Classified as 0,1,2, ≥3.
- **Pregnancy estimated start date:** As I did not have gestational age data, I needed to estimate pregnancy start. I estimated pregnancy start as 42 weeks before child date of birth.
- **HIV viral load:** Categorical variable. Classified as <1000 copies/mL, ≥1000 copies/mL, or no viral load record. Defined closest to child date of birth and pregnancy start for Chapters 4 and 5 respectively. The window periods around these definitions are described in respective chapters.
- **CD4 cell count:** Categorical variable. Classified as <350 cells/µl, ≥350 cells/µl or no CD4 cell count record. Defined closest to child date of birth and pregnancy start for Chapters 4 and 5 respectively. The window periods around these definitions are described in respective chapters.
- **Death during analysis period:** Binary variable (as yes/no) classified using date of death recorded in the WCPHDC. This only includes maternal deaths recorded in the WCPHDC, which are those that occur in a public health facility. Mothers with a date of death and an

indicator of conflicting evidence (predefined within the WCPHDC) against death recorded in the WCPHDC were assumed not to have died.

2.6.2. Child variables

- **Sex at birth:** Categorical variable. Categorised as male/female, as reported in the WCPHDC.
- **Birth weight:** Categorical variable. Classified as foetal macrosomia (≥4000g); normal (2500 – <4000g); low (1500 – <2500g); very low (1000 – <1500g); extremely low (<1000g). In line with a birth weight validation study, child birth weights <350g (if child did not die during the neonatal period) or >6000g were considered to be implausible and coded as missing (N=969 (0.2%) of the overarching cohort) (155).
- **Multiple pregnancy status:** Binary variable. Classified as yes/no, as recorded in the WCPHDC.
- **Season of birth:** Categorical variable. Based on month of birth. Categorised as Summer (December, January, February), Autumn (March, April, May), Winter (June, July, August), Spring (September, October, November).
- **Area of residence:** Categorical variable. For modelling purposes, I used suburb of residence, as recorded in the WCPHDC. For descriptive purposes, I categorised suburb into Metropolitan (City of Cape Town) and non-Metropolitan (all other suburbs).
- **Death during analysis period:** a) Binary variable. Classified as yes/no using date of death recorded in the WCPHDC. As with mothers, this only includes child deaths recorded in the WCPHDC, which are those that occur in a public health facility. Children with a recorded date of death but an indicator of conflicting evidence (predefined within the WCPHDC) against death recorded in the WCPHDC were considered not to have died; b) date variable – used to determine end of follow-up date for children that died before date of first HIV evidence or the end of follow-up period.

2.6.3. Infectious disease hospitalisation variables

I extracted the following variables relating to hospitalisations due to infectious disease, by child age three years (i.e. their third birthday).

- **Age at admission:** Categorical variable. Categorised as ≤6 days, 7 – 27 days, 28 days – 12 months, >12 months – 24 months, > 24 months – 36 months.
- **Admission diagnoses/cause of admission:** Cause of infectious disease hospital admissions were classified within the WCPHDC using International Classification of Diseases 10th Revision (ICD-10) codes in consultation with clinical paediatric infectious disease specialists (156). The infectious disease categories that I considered in my analyses throughout this thesis were LRTIs (including influenza, viral, bacterial and congenital pneumonia, and bronchitis), diarrhoea, meningitis, and tuberculous meningitis (TBM) as they have been reported to be among the leading causes of infectious diseases in the WC (157,158). LRTI and diarrhoea admissions are also monitored as national indicators of child health in SA. The list of ICD-10 codes that were used to infer these infectious disease categories is included in Appendix Table 2.1. Infectious disease outcomes (i.e. assignment of ICD10 codes) were based on the assessment of the treating clinician which includes both clinical features and microbiological and other diagnostic tests and radiology, if these were done. LRTI cases are confirmed with chest radiography. For diarrhoea, tests for common diarrhoea associated complications (e.g. metabolic disturbances) are done. Most viral meningitis cases are diagnosed clinically and with cerebrospinal fluid (CSF) findings, while bacterial meningitis cases are mostly microbiologically confirmed. TBM cases are mostly probable cases that have clinical, imaging and CSF findings consistent with TBM. 20 – 30% of TBM cases will be microbiologically confirmed. It was possible for children to have multiple diagnoses for each infectious disease admission. If there were multiple diagnoses for an admission, the primary diagnoses was selected in the order of TBM, meningitis, LRTI, and diarrhoea. I used this order because TBM and meningitis are more specific diagnoses (as they were likely to have had laboratory tests done and have CSF findings), so if there was evidence for them then they were likely to be the primary cause. It's also more likely that a child would have diarrhoea secondary to TBM for e.g., as opposed to the other way around. Furthermore, the order of primary diagnoses meant that in a case with dual diagnosis, the condition with the most severe long term

consequences was put first (TBM and meningitis are likely to have the most severe long term neurological function consequences).

- **Number of infection-related hospital admissions per child up to age 3 years:** Categorical variable. Categorised as 1, 2, 3 ≥4
- **Length of hospital stay:** Numerical variable. Measured in days using hospital admission and discharge dates.
- **Admission facility type:** Categorical variable. Recorded in WCPHDC as district, central, regional, specialised or tertiary hospital and recategorised as tertiary/non-tertiary hospital. Admission facility type serves as an indication of severity of disease or location of residence as children in the Cape Metro have greater access to tertiary facilities.
- **ICU admission:** Binary variable. Classified as yes/no, as recorded in the WCPHDC.
- **Death during admission:** Binary variable. Classified as yes/no, as recorded in the WCPHDC.

2.7. Missing data

The frequency and proportion of missing data for each variable is described in each analysis chapter. Individuals with missing data for the variables maternal age at delivery, child sex, child birth weight, suburb of residence, multiple pregnancy status, or parity were retained in the data set, but excluded from analyses when the variable for which they had missing data was included as a covariate. The proportion of missing data across all these variables combined was 2.4%, substantially less than 5%. The potential impact of missing data in these variables is therefore likely negligible, warranting complete case analysis for modelling purposes (159). For variables maternal ART start, viral load, and CD4 count, which had a higher proportion of missing data (>3%) and for which I could not distinguish whether the data was missing due to it not being recorded within the WCPHDC or because individuals had not started ART or had their viral loads or CD4 counts measured, I recorded a “no evidence” category for use within analyses. Alternative methods to complete case analysis include multiple imputation, where missing data in an analysis are imputed into multiple datasets (using their estimated predictive distribution) which are then used in analysis with estimates finally being combined using a multiple imputation combining rule; inverse probability weighting, where cases with complete data are weighted by the inverse of their estimated

probability of being complete and population estimates are replaced by weighted estimates; and maximum likelihood-based methods, where all available data is used to estimate the population parameters with the highest probability of resulting in the available sample data (160,161). The advantages and disadvantages of these alternative methods are described below in Table 2.4

Table 2.4: Advantages and disadvantages of methods to deal with missing data

Method	**Advantages**	**Disadvantages**
Multiple imputation	▪ Uses data in incomplete cases for analyses (160). ▪ Auxiliary variables can be used to improve the efficiency of multiple imputation by being a source of information about missing values (162).	▪ Imputation models are susceptible to misspecification as the proportion of missing data increases (162). ▪ The imputation model needs to have the same structure as the analysis model (e.g. contain random effects). Imputation may therefore need to be done separately for different analyses and structural deficits in the imputation models can cause bias (163).
Inverse probability weighting	▪ The missingness model does not have to have the same structure as the analyses model (163). ▪ Can deal with both missing data and unequal sampling fractions concurrently (163).	▪ Weights are determined using data in complete cases only. Consequently, large weights can be assigned to extreme data values, leading to high variance in weighted estimates (160).
Maximum likelihood-based methods	▪ Produces unbiased estimates with small standard errors (164).	▪ Requires specialised software (164). ▪ Good estimates rely on large samples (164).

2.8. Ethical considerations

This analysis was approved by the University of Cape Town Human Research Ethics Committee (REF 101/2021) (Chapter 2 appendix).

A waiver of informed consent was obtained for this research as all data had already been routinely collected by health services and no participant recruitment was required.

2.9. Sample size

As this is a province-wide analysis including all available data, no a priori sample size calculation was performed.

CHAPTER 3. HIV EXPOSURE CLASSIFICATION

3.1. Chapter overview

As discussed in the literature review (Chapter 1 – section 1.2.7), the classification of child HIV exposure and HIV infection status is complex and susceptible to misclassification, particularly through missed maternal HIV acquisition (child misclassified as HIV-unexposed) and missed child HIV infection (child misclassified as HIV-uninfected). This chapter utilises a simplified version of standardised definitions, proposed by The DECIPHER Project, to a) classify *in utero* child HIV exposure and HIV infection status and b) assess the retrospective applicability of these definitions to routine longitudinal mother and child healthcare data. These definitions are then applied and referred to within each analysis chapter of the thesis.

The work within this chapter has been submitted as a brief report to The Pediatric Infectious Disease Journal. The brief report has undergone review and I have submitted a revised manuscript which is currently under review.

de Beer ST, Davies MA, Phelanyane F, Jones HE, Ingle SM, Eley B, Anderson K, Heekes A, Kalk E, Mendelsohn A, Boulle A, Slogrove AL. The retrospective implementation of standardised *in utero* HIV exposure definitions using routinely collected public sector data across the Western Cape Province, South Africa. Submitted to the Pediatric Infectious Disease Journal (PIDJ) in July 2023. *The manuscript has undergone review and I have submitted a revised manuscript as of March 2024.*

The work included from the submitted brief report has been reformatted to match the format, styles, numbering, and referencing used throughout the thesis.

Role of the candidate: I was responsible for the data management to construct the dataset for analyses. I carried out the analyses, drafted the brief report, incorporated feedback from co-authors, finalised the brief report, submitted it for publication and revised the manuscript in response to peer-review comments.

3.2. Introduction

To minimise misclassification and improve interpretation and comparability of findings within and across studies, The DECIPHER Project proposed standardised definitions, based on knowledge of maternal and child HIV testing, infant antiretroviral prophylaxis and HIV exposure through breastfeeding, to infer certainty of the absence of HIV infection in children HEU and absence of *in utero* HIV exposure in children HIV-unexposed uninfected HUU (137). These definitions are especially important for determining the role of *in utero* HIV exposure relative to key outcomes such as infectious disease hospitalisations, growth and neurodevelopment (24,96,165). The definitions were primarily designed for use in prospective observational studies; with retrospective routine healthcare data it's possible that not all the data required to apply the full standardised definitions will be available. This chapter aimed to a) assess the retrospective applicability a of simplified version of the DECIPHER definitions (Table 3.1) (the simplification is described in section 3.3.3) to the routine longitudinal mother and child healthcare data used within this thesis, and b) classify *in utero* child HIV exposure and HIV infection status and assess how the certainty of these classifications change over time. I classified certainty of the absence of HIV infection among children with *in utero* HIV exposure and the absence of *in utero* HIV exposure and HIV infection among children HUU, at ages one and three years, and at the time of first hospitalisation for children hospitalised with infectious diseases by their third birthday (age $\leq$3 years).

3.3. Methods

3.3.1. Data source

This was a retrospective, population-based analysis using digitised routine maternal and child healthcare data housed within the WCPHDC (148). The WCPHDC has been discussed in further detail in Chapter 2 - section 2.3.

3.3.2. Study participants

The inclusion and exclusion criteria for children in this analysis were described in Chapter 2 – section 2.4. In brief, I included all children identified electronically as having been born alive in one of the WC health facilities reporting to the WCPHDC between January 2008 and December 2018. As in all chapters of this thesis, children were excluded if they were not electronically linked to their mothers, their mothers' HIV first evidence date was >10 weeks postnatally, or they or their mothers had data inconsistencies. In this chapter, children were also excluded if they were known to have HIV at birth (up to age 10 weeks) through *in utero* or intrapartum HIV transmissions, or their HIV first evidence date was after 10 weeks of age with an unknown time of HIV acquisition (i.e. they did not have a negative HIV test result after age 10 weeks) so that children living with/potentially living with HIV were not included in the classification of children HEU and HUU (Figure 3.1). Follow-up time for children was from date of birth until the earliest date of last negative HIV test result if diagnosed with HIV, death, or age three years. Therefore, at each timepoint I excluded a) children whose first evidence of having HIV was after the timepoint of interest, but whose timing of HIV acquisition was unknown (i.e. They never had an HIV negative test result between the timepoint of interest and their date of first HIV evidence) and b) children who had evidence of HIV or date of death before the timepoint of interest.

3.3.3. Procedures and measurements

For this analysis, I utilised data on child date of birth, maternal and child laboratory test results (HIV PCR, HIV antigen/antibody and/or HIV-Rapid tests), maternal and child HIV first evidence dates, child infectious disease hospitalisation admission and discharge dates and, if the mother or child died during the study period, date of death. Children were classified as a) HIV unexposed if their mothers had no evidence of HIV or the first evidence of maternal HIV was after the child's third birthday and b) HIV exposed *in utero* if the mother's first evidence of HIV was ≤10 weeks after the infant's date of birth. Children diagnosed with HIV were assumed to be without HIV until the date of their last negative HIV test.

As this was a retrospective analysis of routine care data and there is limited data on breastfeeding and infant antiretroviral prophylaxis in the WCPHDC, both of which are

required to use the full DECHIPHER definitions, I simplified the definitions by omitting the criteria that require infant antiretroviral prophylaxis and breastfeeding data. Furthermore, point-of-care HIV tests are not routinely digitised but antenatal testing rates are high (>95%) in this setting (166), therefore I assumed that mothers with unknown HIV status were without HIV. I therefore classified children whose mothers had no record of a negative HIV test result as HUU low certainty, as opposed to unclassified. The simplified DECIPHER definitions after implementing these simplifications are described in Table 3.1. I used the most recent negative HIV test result for children and mothers who had a HIV test record in the WCPHDC, up until 31 December 2021, and applied the simplified DECIPHER definitions, at each timepoint of interest, to classify certainty of the presence and absence of *in utero* HIV exposure without HIV infection.

I described HIV exposure status and certainty about this status (as high, medium, low or no certainty), at ages one and three years, after first excluding any children who died before these time points. For all children with an infectious disease hospitalisation before age 3 years, I also described exposure status and certainty at date of hospitalisation. I described exposure status and certainty both overall and by period of birth (categorised as 2008 – 2011, 2012 – 2015, and 2016 – 2018). As per the DECIPHER definitions, the 'no certainty' classification only applied to children HEU. Because the simplified DECIPHER definitions classified children HUU whose mothers had no record of a negative HIV test result as HUU low certainty, I further described the proportion of children HUU low certainty whose mothers had an HIV test result and those whose mothers had an unknown HIV status.

Table 3.1: Simplified DECIPHER definitions for classification of children as HEU and HUU

Simplified DECIPHER Definitions

Children HEU:

- **High certainty:** Child of a mother known to have HIV AND child tested HIV-negative (antibody or nucleic acid test) at ≥6 weeks of age AND at/after study outcome measurement
- **Moderate certainty:** Child of a mother known to have HIV AND child tested HIV-negative (antibody or nucleic acid test) at least once at age ≥6 weeks but before study outcome measurement
- **Low certainty:** Child of a mother known to have HIV AND child tested HIV-negative by nucleic acid test at <6 weeks of age only
- **No certainty that the child is HIV uninfected:** Child of a mother known to have HIV AND child never tested for HIV

Children HUU:

- **High certainty:** Child of a mother who tested HIV-negative by any test type at/after the time of study outcome measurement AND child tested HIV-negative by any test type at least once at any time
- **Moderate certainty:** Child whose mother's test meets high certainty criteria but child has never tested for HIV
- **Low certainty:** Child whose mother tested HIV-negative during pregnancy but before study outcome measurement OR mother has no record of a HIV-negative test and no evidence of HIV

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected

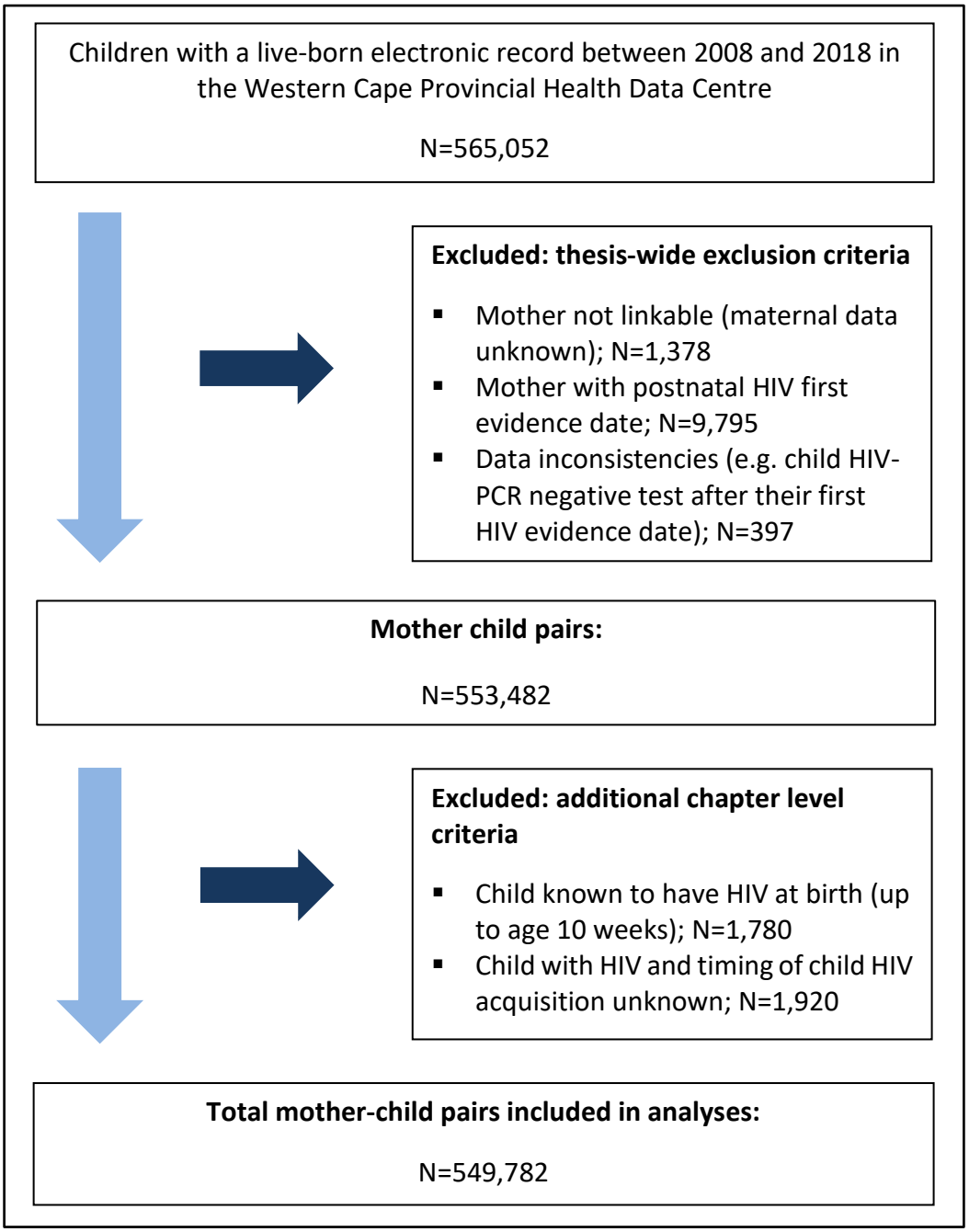


Figure 3.1: Flow diagram of mother-child pairs meeting the inclusion and exclusion criteria for analyses in Chapter 3

3.4. Results

Between January 2008 and December 2018, there were 565,052 live-born children, with electronically-recorded births at a WC public health facility. Of these children, I excluded 1,378 (0.2%) who were unlinked to a maternal record, 9,795 (2.0%) whose mothers had a HIV first evidence date at >10 weeks postpartum, 397 (0.1%) with data inconsistencies, 1,780 (0.3%) who were known to have HIV at birth, and 1,920 (0.3%) with unknown timing of infant HIV-acquisition (Figure 3.1). Of the 549,782 children eligible for inclusion, 84,611 (15.4%) and 465,171 (84.6%) were classified as HIV-exposed but not uninfected (i.e. HEU) and HIV-unexposed uninfected (i.e. HUU) at birth (*in utero*) for the full period of analyses (2008 – 2021). By period of birth, the proportion of children HEU at birth increased from 10.2% (2008-2011) to 15.4% (2012-2015) to 18.2% (2016-2018). Among children classified as HEU, the overall level of certainty was moderate or high for 64.1% at age 1 year, 64.0% at age 3 years, and 89.8% at time of hospitalisation (Figure 3.2; Table 3.2). Among children HUU, the overall level of certainty was low for 93.6% at age 1 year, 95.0% at age 3 years, and 92.8% at hospitalisation. The proportion of children classified HUU with low certainty whose mothers had a negative HIV result and whose mothers had an unknown HIV status is described in Appendix Table 3.1.

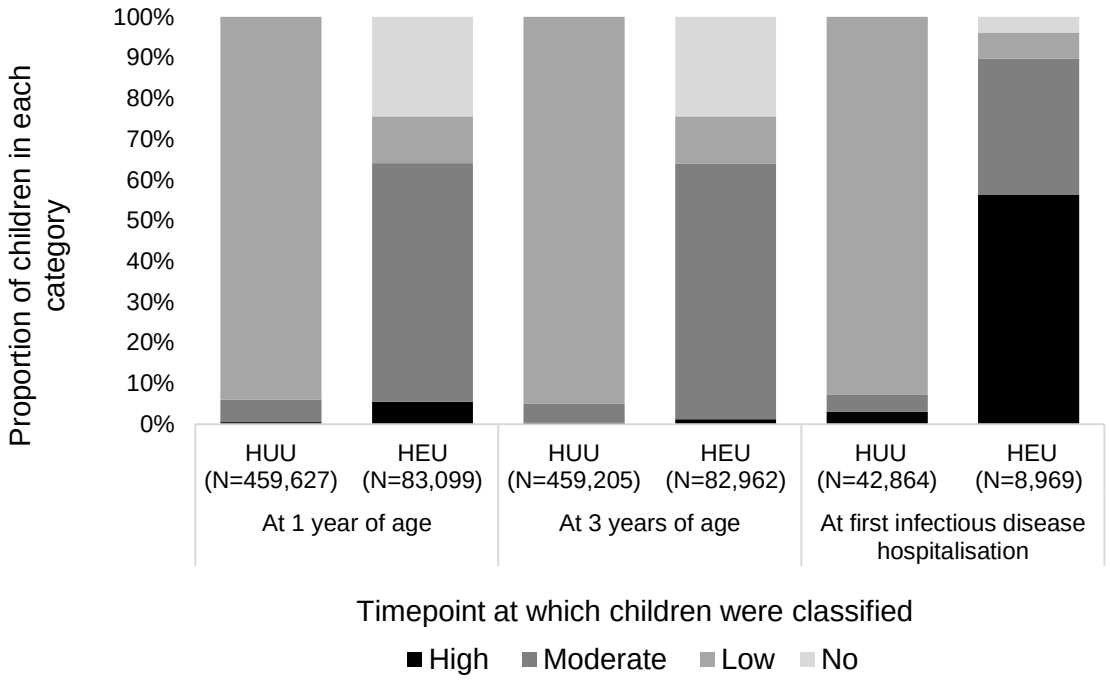


Figure 3.2: Classification of certainty of HIV exposure status in children born to mothers with and without HIV, in Western Cape, South Africa (2008-2018), at age one (N=542,726), age three (N=542,167), and at first infectious-cause hospitalisation (N=51,833) [¥]

[¥] At all three timepoints I included children not known to have HIV and excluded children whose HIV first evidence after the timepoint of interest but with unknown timing of acquisition. Only children who survived to ages 1 and 3 years were considered for each timepoint respectively.

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected

Table 3.2: Classification of certainty of HIV exposure status in children born to mothers with and without HIV, in Western Cape, South Africa (2008-2018), at age one (N=542,726), age three (N=542,167), and at first infectious-cause hospitalisation (N=51,833) [¥]

	High certainty N (%)	Moderate certainty N (%)	Low certainty N (%)	No certainty N (%)
At 1 year of age				
Children HUU (N=459,627)	2,433 (0.5)	27,003 (5.9)	459,627 (93.6)	Not applicable
Children HEU (N=83,099)	4,627 (5.6)	48,629 (58.5)	9,552 (11.5)	20,291 (24.4)
At 3 years of age				
Children HUU (N=459,205)	1,830 (0.4)	21,163 (4.6)	436,212 (95.0)	Not applicable
Children HEU (N=82,962)	1,008 (1.2)	52,124 (62.8)	9,544 (11.5)	20,286 (24.5)
At first infectious disease hospitalisation				
Children HUU (N=42,864)	1,288 (3.0)	1,812 (4.2)	39,764 (92.8)	Not applicable
Children HEU (N=8,969)	5,054 (56.4)	2,993 (33.4)	577 (6.4)	345 (3.9)

[¥] At all three timepoints I included children not known to have HIV and excluded children whose first evidence of HIV was after the timepoint of interest but with unknown timing of acquisition. Only children who survived to ages 1 and 3 years were considered for each timepoint respectively.

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected

The certainty of HEU classification improved over time, by calendar year of child birth (Figure 3.3; Table 3.3); among children HEU born in 2008 to 2011, the level of certainty at age 1 year was moderate for 28.0% and there was no certainty for 63.7%, compared to 69.7% and 7.9% respectively for children born in 2016 to 2018. For children HUU, the proportion classified with low certainty increased overtime from 90.7% among children born in 2008 to 2011 to 95.8% among children born between 2016 to 2018, at age 1. Corresponding increasing and decreasing patterns in certainty were observed for children HEU and HUU, respectively, at age 3 years and at the time of first infectious disease admissions.

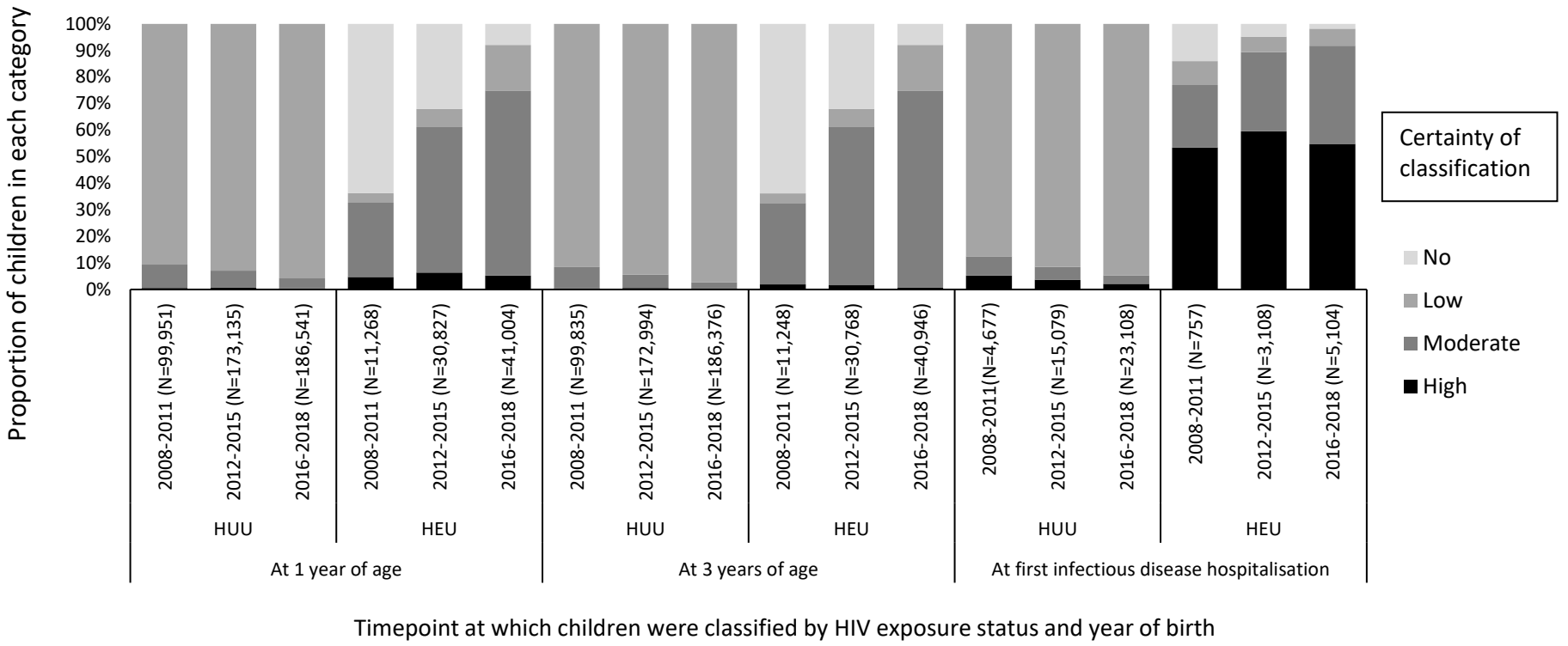


Figure 3.3: Certainty of HIV exposure status in children born to mothers with and without HIV, in Western Cape, South Africa (2008-2018), at age one (N=542,726), age three (N=542,167), and at first infectious-cause hospitalisation (N=51,833), by year of birth [¥]

[¥] At all three timepoints I included children not known to have HIV and excluded children whose first evidence of HIV was after the timepoint of interest but with unknown timing of acquisition. Only children who survived to ages 1 and 3 years were considered for each timepoint respectively.

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected

Table 3.3: Certainty of HIV exposure status in children born to mothers with and without HIV, in Western Cape, South Africa (2008-2018), at age one (N=542,726), age three (N=542,167), and at first infectious-cause hospitalisation (N=51,833), by year of birth[¥]

Birth year	2008 – 2011	2012 – 2015	2016 – 2018	Total
		At 1 year of age		
CHILDREN HUU – N	99,951	173,135	186,541	459,627
High certainty N (%)	556 (0.6)	1,147 (0.7)	730 (0.4)	2,433 (0.5)
Moderate certainty N (%)	8,756 (8.8)	11,152 (6.4)	7,095 (3.8)	27,003 (5.9)
Low certainty N (%)	90,639 (90.7)	160,836 (92.9)	178,716 (95.8)	430,191 (93.6)
CHILDREN HEU – N	11,268	30,827	41,004	83,099
High certainty N (%)	527 (4.7)	1,977 (6.4)	2,123 (5.2)	4,627 (5.6)
Moderate certainty N (%)	3,156 (28.0)	16,882 (54.8)	28,591 (69.7)	48,629 (58.5)
Low certainty N (%)	403 (3.6)	2,098 (6.8)	7,051 (17.2)	9,552 (11.5)
No certainty N (%)	7,182 (63.7)	9,870 (32.0)	3,239 (7.9)	20,291 (24.4)
		At 3 years of age		
CHILDREN HUU – N	99,835	172,994	186,376	459,205
High certainty N (%)	497 (0.5)	899 (0.5)	434 (0.2)	1,830 (0.4)
Moderate certainty N (%)	7,911 (7.9)	8,846 (5.1)	4,406 (2.4)	21,163 (4.6)
Low certainty N (%)	91,427 (91.6)	163,249 (94.4)	181,536 (97.4)	436,212 (95.0)
CHILDREN HEU – N	11,248	30,768	40,946	82,962
High certainty N (%)	214 (1.9)	507 (1.7)	287 (0.7)	1,008 (1.2)
Moderate certainty N (%)	3,453 (30.7)	18,296 (59.5)	30,375 (74,2)	52,124 (62.8)
Low certainty N (%)	401 (3.6)	2,097 (6.8)	7,046 (17.2)	9,544 (11.5)
No certainty N (%)	7,180 (63.8)	9,868 (32.1)	3,238 (7.9)	20,286 (24.5)
		At first infectious disease hospitalisation		
CHILDREN HUU – N	4,677	15,079	23,108	42,864
High certainty N (%)	246 (5.3)	561 (3.7)	481 (2.1)	1,288 (3.0)
Moderate certainty N (%)	335 (7.2)	729 (4.8)	748 (3.2)	1,812 (4.2)
Low certainty N (%)	4,096 (87.6)	13,789 (91.5)	21,879 (94.7)	39,764 (92.8)
CHILDREN HEU – N	757	3,108	5,104	8,969
High certainty N (%)	405 (53.5)	1,851 (59.6)	2,798 (54.8)	5,054 (56.4)
Moderate certainty N (%)	178 (23.5)	929 (29.9)	1,886 (37.0)	2,993 (33.4)
Low certainty N (%)	68 (9.0)	179 (5.8)	330 (6.5)	577 (6.5)
No certainty N (%)	106 (14.0)	149 (4.8)	90 (1.8)	345 (3.9)

[¥]At all three timepoints I included children not known to have HIV and excluded children whose first evidence of HIV was after the timepoint of interest but with unknown timing of acquisition. Only children who survived to ages 1 and 3 years were considered for each timepoint respectively.

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected

3.5. Discussion

This is, to my knowledge, the first analysis to apply DECIPHER's standardised *in utero* HIV exposure definitions to routinely-collected data. The definitions were primarily designed for use in prospective observational studies and clinical trials in diverse settings but can be applied retrospectively to existing cohorts (137). This analysis found that, the proportion of children born HEU in the WC increased overtime, by period of birth year, with the majority being classified with moderate or high certainty. Furthermore, the certainty of HEU classification improved over time. The majority of children HUU were classified with low certainty and this proportion increased overtime.

The DECIPHER team evaluated the feasibility of the standardised definitions by applying them retrospectively to individual-level data available from the United States based Surveillance Monitoring for ART Toxicities (SMARTT) cohort (137). They found that of children HEU, 69%, 2% and 29% met high, moderate and low certainty, respectively. In my study setting, 64%, 64% and 90% of children HEU were classified with moderate or high certainty at ages one and three years and at the time of infectious disease hospitalisation, respectively. These results can be partially explained by the WC vertical transmission prevention guidelines and coverage of infant HIV testing (31,35).

WC guidelines recommended that all infants who are HIV-exposed receive routine HIV testing at birth (from 2015), at six/ten weeks, nine months and 18 months of age (if not already known to have HIV). In 2020, guidelines were updated to include a test at six months instead of nine months (32). Uptake of six to ten week infant HIV-PCR testing in WC settings has been reported to range from 77%-87%, post 2013 (167,168). Given that HEU classification with moderate certainty requires a negative HIV-PCR test ≥6 weeks of age, I would expect a large portion of my HEU cohort to at least be classified with moderate certainty at both ages 1 and 3 years. High certainty HEU classification requires a negative test at/after outcome measurement. Uptake of 18-month infant HIV testing is poor in the WC (<25%) (108,168), which is reflected in my finding of a low proportion of children HEU classified with high certainty at age 1 year (6%). As 18 months of age is the last timepoint for routine HIV testing of children HEU, most children's last HIV negative test would be before 3 years of age, unless illness after this date prompted additional testing. Therefore, the majority of children HEU

could be classified with at most moderate certainty at age 3 years. Consequently, I found a decrease in the proportion of children classified as HEU high certainty by age 3 years, relative to age 1 year. It is routine practice for ill children, regardless of HIV exposure status, to be tested for HIV upon admission to hospital. This explains why most hospitalised children HEU were classified with high certainty at admission.

The classification of child HIV exposure and infection status by certainty levels provides transparency of potential misclassifications and enables sensitivity analyses that are restricted to children classified with higher certainty. Table 3.4 highlights the advantages and disadvantages of restricting analyses, comparing health outcomes in children HEU to children HUU, to children classified HEU / HUU with high or moderate certainty.

Table 3.4: Advantages and disadvantages of restricting analyses, comparing health outcomes in children HEU to children HUU, to children classified HEU/HUU with high or moderate certainty.

	Advantages	**Disadvantages**
1.	Restricts the sample to children that are less likely to be misclassified as HEU or HUU – i.e. increases the sensitivity of the HIV exposure classification.	Excluding children classified with low certainty reduces the sample size and can thereby reduce the statistical power of the analyses to observe differences between HEU and HUU groups.
2.	The reported study estimates are more likely to be reflective of the true population estimates ▪ If children with HIV were classified as HEU low certainty then the study estimate would have been overestimated. ▪ If children HEU were classified as HUU low certainty the study estimate would have been underestimated.	Excluding children classified with low certainty can introduce biases into the study. ▪ Children classified with low may be a vulnerable group of children who have limited access to care. ▪ Children classified with medium/high certainty may be more likely to have been hospitalised and as a result have HIV test results. Study estimates may be biased towards or away from the null (i.e. no difference between exposure groups) depending on whether the exclusion of children classified with low certainty differentially impacts children HEU or HUU.
3.	Study results may be more comparable to that of other studies in which children are classified with moderate or high certainty.	Excluding children classified with low certainty may result in an important vulnerable group at high risk of admission being excluded from analyses.

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected

This analysis has several limitations. Rapid point-of-care HIV test results have only recently been digitised in the WCPHDC for a small proportion of mothers and infants and were therefore not available. This particularly meant that there were a small proportion of HIV test results for mothers; consequently, most children HUU were classified with low certainty as being HIV-unexposed at ages 1 and 3 years. This would have also resulted in the underestimation of the proportion of children HEU classified with high certainty at these ages. However, efforts are currently underway to commence digitisation of point-of-care HIV test results. A further limitation is that the electronic patient administrative system, with a 'unique' provincial identifier, was progressively implemented over time with complete coverage of facilities with patient registration systems only being achieved in October 2017 (148). This may have resulted in missing electronic records of infant HIV-PCR tests in the earlier years of the analysis with resultant misclassification of certainty. This is evident in the reduction over time of children classified HEU with no certainty. It is also possible that infants were allocated alternative 'unique' provincial identifiers as they got older or that they moved/relocated and were tested in other provinces, resulting in 'missing' HIV test data.

An additional limitation is that I excluded women with postnatal HIV acquisition. The DECIPHER project has not yet developed definitions for postnatal HIV exposure that will be more complex considering infant age at maternal postnatal HIV-acquisition and duration of HIV-exposure via breastfeeding. This is an important group of women whose children are exposed to a high viral load via breastmilk and are at a higher risk of acquiring HIV, compared to children of mothers with chronic HIV (169). However, they account for a relatively small proportion of all HIV exposure (in my dataset 2% of all children were born to mothers with a postnatal HIV first evidence date, compared to 15% of all children with *in utero* HIV exposure).

Conclusions

In conclusion, a simplified version of DECIPHER's standardised child HIV *in utero* exposure definitions is suitable for retrospective use in settings with routine, linked mother-child data. I found that simplified DECIPHER classifications provide transparency around potential misclassification and inform the interpretation and comparability of study results. Although this analysis focused specifically on infectious diseases, these definitions will be applicable to analyses with other outcomes of interest, e.g. growth and neurodevelopment. Moreover, the

definitions may be of value to data consolidation repositories, such as the WCPHDC, in classifying certainty levels of infant/child antenatal HIV exposure and infection status, enabling consistency in future research studies utilising the same data source. Additionally, digitisation of point-of-care tests would add considerably to classification certainty when analysing routine health datasets such as those from the WCPHDC. As these definitions were applicable to the dataset used for analyses in this thesis, they were used to classify *in utero* HIV exposure and infection status at timepoints relevant to each analyses chapter.

CHAPTER 4. CHANGE IN HIV-RELATED CHARACTERISTICS OF CHILDREN HOSPITALISED WITH INFECTIOUS DISEASES

4.1. Chapter overview

In Chapter 3, I used a simplified version of DECIPHER's HIV exposure and infection status definitions to classify the *in utero* HIV exposure and infection status of children at ages one and three years and at the time of first infectious disease hospitalisation. Among children classified as HEU, the level of certainty was moderate or high for 90% of children at the time of hospitalisation. As these definitions were seen to be applicable (i.e. could be used to classify HIV exposure and infection status) to the routine healthcare data in my dataset, I have used the classification of *in utero* HIV exposure and infection status at time of hospitalisation, determined in Chapter 3, for this chapter (Chapter 4).

With the scale-up of HIV VTP in SA over the last two decades, there has been a shift in the HIV-related population profile of children, as seen in Chapter 3 with the increase in the proportion of children HEU over time. Furthermore, as described in Chapter 1, evidence suggests that HIV exposure is associated with infectious disease morbidity among children without HIV. In this chapter, I describe temporal changes in HIV-related characteristics of children, aged ≤3 years, with infectious disease hospitalisations across the WC province.

The work described in this chapter was also published as a peer reviewed journal article in the Journal of the International AIDS Society as part of the supplement "Understanding challenges and optimising outcomes of children with perinatal HIV exposure" (Chapter 4 appendix):

de Beer ST, Slogrove AL, Eley B, Ingle SM, Jones HE, Phelanyane F, Anderson K, Kalk E, Boulle A, Davies MA. Change in HIV-related characteristics of children hospitalised with infectious

diseases in Western Cape, South Africa, 2008-2021: a time trend analysis. J Int AIDS Soc. 2023 Oct;26(Suppl 4):e26151.

The work included from the published journal article has been reformatted to match the format, styles, numbering, and referencing used throughout the thesis.

Role of the candidate: I was responsible for the data management to construct the dataset for analyses. I carried out the analyses, drafted the manuscript, incorporated feedback from co-authors, finalised the manuscript, submitted it for publication, and revised the manuscript in response to peer-review comments.

4.2. Introduction

As highlighted in Chapter 1, infectious diseases are a leading cause of paediatric morbidity and mortality and place a burden on public healthcare services, particularly those that are already stretched (6,74,130,170). Evidence suggests that both children with HIV infection and children HEU may be more likely to have infectious diseases compared to children HUU. For example, between 1992 and 1997, HIV prevalence among paediatric admissions at an urban hospital in SA increased from 3% to 20% (171,172), with a related increase in infectious diseases admissions. Furthermore, as discussed in-depth in Chapter 1 (sections 1.2.4 and 1.2.5), children HEU have been reported to have higher risk of infection-related hospitalisations than children HUU (17,24).

In Chapter 1 (sections 1.2.1 and 1.2.2), I described the substantial scale-up and success of HIV VTP in SA which was largely attributable to improved and simplified guideline recommendations resulting in increased access to ART for pregnant and breastfeeding women living with HIV (166). As a brief recap, in 2015 (or 2013 in the WC province of SA), ART became available to all pregnant and breastfeeding women living with HIV, regardless of CD4 count, with the introduction of Option B+ (173). In 2016, ART became universally available to all persons living with HIV, meaning more mothers would have access to ART before their first pregnancy (174). Consequently, SA has seen a shift in the HIV-related profile of children under age 15 years; between 2000 and 2018 HIV prevalence in children decreased by 74% while the proportion who are HEU increased over seven-fold, accounting for 22% of all children (age 0-

14 years) in SA in 2018 (3,47). Furthermore, ART coverage in pregnancy in SA was 96% in 2019 (175), meaning that most children HEU are exposed to ART during gestation. Studies have previously used HIV prevalence among hospitalised children as an indicator of the HIV epidemic's impact on child health services (172,176). However, with the growing population of children HEU, and evidence that *in utero* HIV and ART exposure are also associated with child health outcomes in the absence of child HIV infection (3), it is also important to measure these characteristics, to more comprehensively understand the effect of the HIV epidemic on child health services.

I aimed to describe, at a provincial-level, a) non-HIV related characteristics and b) the temporal changes in HIV-related characteristics (child HIV infection, child HIV exposure, child exposure to maternal ART, timing of exposure to maternal ART, maternal CD4 count, and maternal viral load) of children hospitalised with one of four infectious diseases - LRTI, diarrhoea, meningitis, and TBM (section 2.6.3) - from 2008 – 2021, using longitudinal individual-level routine care data from the WCPHDC.

4.3. Methods

4.3.1. Study design, data source and study setting

Details of the study design, data source, and study setting have been described in Chapter 2 – sections 2.2 and 2.3.

4.3.2. Study participants

The inclusion and exclusion criteria for the analyses in this chapter are described in Chapter 2– section 2.4. I used routinely collected electronic data to identify children born in the WC between 2008-2018, with a known live birth outcome, who had records of infectious disease hospitalisation aged ≤3 years from January 2008 to December 2021. As in all chapters of this thesis, children were excluded if: they were not electronically linked to their mothers, their mothers' HIV first evidence date was >10 weeks postnatally, or they or their mothers had data inconsistencies. Compared to Chapter 3 which included both hospitalised and non-hospitalised children, this chapter only included children hospitalised with one of the 4

abovementioned infectious disease by age 3 years. As described in Chapter 2 (Table 2.2), another key difference is that this chapter included all children with a known positive HIV status at the time of hospitalisation (children with unknown timing of HIV acquisition relative to hospital admission were excluded), whereas in Chapter 3 children were excluded once they had evidence of living with HIV. The reason for this key difference is that this chapter describes the change in the proportion of hospitalised children with HIV over time, whereas Chapter 3 defined HIV exposure status among children not known to have HIV. The number of children included and excluded for this chapter is shown in Figure 4.1. I compared the key non-HIV related characteristics of those included in vs. excluded from these analyses to assess potential selection bias in my sample (Appendix Table 4.1).

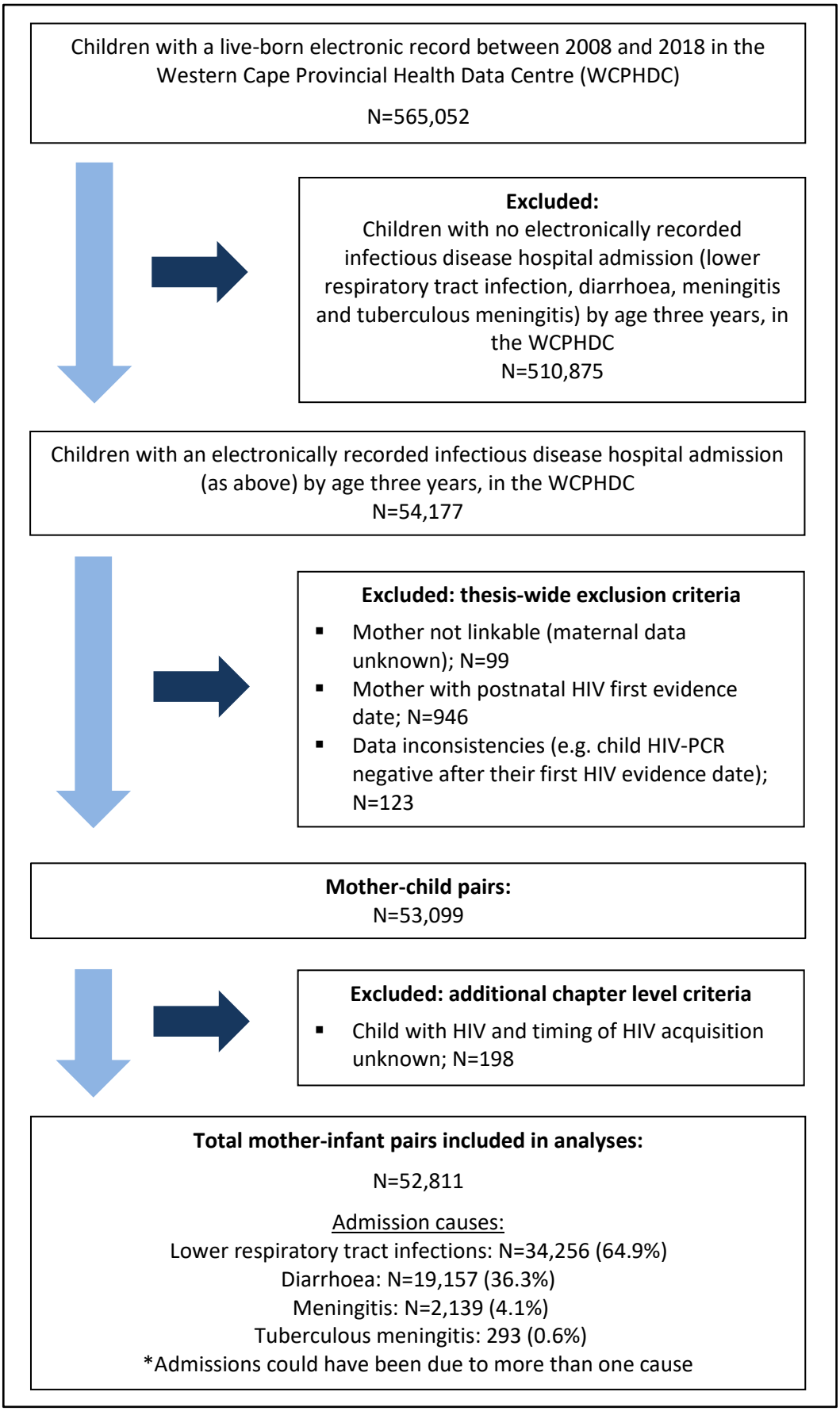


Figure 4.1: Flow diagram of mother-child pairs meeting the inclusion and exclusion criteria for analyses in Chapter 4

4.3.3. Procedures and measurements

The overarching data cleaning, management and extraction that I carried out for this chapter is described in Chapter 2 – section 2.5. For this chapter, I used data from the WCPHDC on child sex, child date of birth, child birth weight, multiple pregnancy status, and, if the mother or child died in-facility during the study period, date of death (could be before or after hospitalisation for mother – up to child age 3 years, but only after hospitalisation for children) to describe non-HIV related characteristics of children and mothers. Definitions/categorisation of these variables are described in Chapter 2 – section 2.6. Hospitalisation data included admission date, discharge date, and causes of admission (of the four infectious diseases of interest). For children diagnosed with HIV, I used child's HIV first evidence date. The categorisation of *in utero* HIV exposure status and HIV infection status of each child at infectious disease hospitalisation discharge date as CWH, HEU, or HUU, was described and presented in Chapter 3. Children who tested positive were considered HIV negative until their last negative HIV test and to have an unknown HIV status thereafter until date of first HIV evidence. CWH whose mothers were not known to be living with HIV (N=74) were included for assessing change in HIV infection status over time, but excluded for the analysis of other HIV-related characteristics.

For mothers with HIV, I used HIV first evidence date, ART start and dispensing dates, CD4 count and viral load measurements/results. These were used to define the following HIV-related variables:

- Timing of maternal HIV first evidence (before pregnancy, during pregnancy, at delivery/postnatally)
- Timing of maternal ART start (before pregnancy, during pregnancy, delivery/postnatally, no ART evidence)
- Child exposure to maternal ART (yes/no: defined by using ART dispensing dates to determine if mothers were on ART at any point between conception and 3 months post-delivery)
- Timing of earliest child exposure to maternal ART (at conception, early/middle gestation (post-conception to three months pre-delivery), late gestation/postnatally (within three

months pre or post-delivery): based on the earliest time point mothers were dispensed ART between conception and 3 months post-delivery)

- Maternal CD4 count (<350 cells/μL, 350 – 499 cells/μL, ≥500 cells/μL: using records closest to delivery, within a 365 day window of delivery)
- Maternal HIV viral load (<1000 copies/mL, ≥1000 copies/mL: using records closest to delivery, within a 365 day window of delivery)

I described these characteristics over time by year of infectious disease hospital admission. For modelling purposes, I further categorised time of hospital admission into periods: January 2008 – April 2013 (Pre-Option B+), May 2013 – August 2016 (Option B+), and September 2016 – December 2021 (Universal ART).

4.3.4. Statistical analyses

I described non-HIV related characteristics of all children and their mothers. For HIV-related characteristics, I first described child HIV and infection status among all hospitalised children. After excluding CWH whose mothers had no evidence of having HIV (N=74), I described timing of maternal HIV first evidence and ART start, and child exposure to maternal ART, for all children HIV-exposed (including CWH). Among children exposed to maternal ART, I described the timing of their earliest exposure to maternal ART. Finally, I described maternal HIV viral load and/or CD4 count closest delivery for mothers who had laboratory records for either of these. Maternal HIV viral loads and/or CD4 counts were described separately for CWH and children HEU.

I described and assessed differences in non-HIV-related child and maternal characteristics, by categorised year of admission, using proportions (categorical variables), and means or medians (continuous variables) with standard deviations or first and third quartiles, for non-skewed and skewed data respectively (assessed using histograms). I plotted trends over time in the proportions of different HIV-specific characteristics among hospitalised children. Statistical evidence for changes in proportions across the three time periods was assessed using univariable logistic and multinomial regression models, for binary and non-binary categorical variables respectively, with the HIV-related characteristic as the dependent

variable and time (periods) as the independent variable. All statistical analyses were done using Stata 17.0 (177,178).

4.4. Results

Between 2008 and 2018, there were 54,177 children born at WC public health facilities who had an electronic hospital admission record for at least one of the four infectious diseases of interest by age three years, of whom 52,811 (97.5%) were included in the analyses for this chapter (Figure 4.1.) Of the 1,366 children that were excluded from these analyses, 69.3% had mothers who had a postnatal HIV first evidence date. The key differences between children excluded from and children included in the analyses were the proportion of in-hospital child deaths by age 3 (2.6% vs. 1.5%), the proportion of children with first evidence of HIV by the time of hospitalisation (5.8% vs. 1.9%), and the proportion of in-hospital maternal deaths by child age three (1.1% vs. 0.5%) (Appendix Table 4.1).

Of the 52,811 admissions, 64.9% of children had a diagnosis of LRTI, 36.5% diarrhoea, 4.1% meningitis and 0.6% TBM (Figure 4.1). The number of annual admissions recorded in the WCPHDC varied substantially during the study period, with 75.5% of all admissions occurring from 2015 onwards (Table 4.1).

Table 4.1: Count and percentage of hospital admissions per year

Admission year	Frequency	%
2008	512	1.0
2009	1,088	2.1
2010	1,338	2.5
2011	1,400	2.7
2012	1,814	3.4
2013	2,878	5.4
2014	3,855	7.3
2015	5,590	10.6
2016	6,786	12.8
2017	8,238	15.6
2018	11,176	21.2
2019	6,276	11.9
2020	1,406	2.7
2021	454	0.9
Total	52,811	–

4.4.1. Non-HIV-related characteristics of children and mothers

Among children included, 56.4% were male and 1.5% died before age three years (Table 4.2). The proportion of admitted children with very low (1000-1499g) and low birth weight (1500-2499g) decreased between the Pre-Option B+, Option B+ and Universal ART periods, from 8.3% to 4.8% to 3.2%, and from 23.3% to 19.0% to 17.0%, respectively. Mean maternal age at delivery remained constant at 27 years throughout, while the proportion of mothers who died by child age three years decreased from 1.0% Pre-Option B+ to 0.5% during Option B+ and 0.4% during the Universal ART period.

Table 4.2: Characteristics of children (and their mothers), born in Western Cape from 2008 – 2018, who had an infectious disease hospital admission (LRTI, diarrhoea, meningitis, TBM), by different ART policy periods (Pre-Option B+, Option B+, Universal ART)

Variable	Total N=52,811 (100%)	Pre-Option B+ (A) N=7,223 (13.7%)	Option B+ (B) N=16,030 (30.4%)	Universal ART (C) N=29,558 (56.0%)
CHILD CHARACTERISTICS				
Sex: n (%)				
Male	29,761 (56.4)	4,052 (56.1)	9,101 (56.8)	16,608 (56.2)
Missing	15 (0.03)	0 (0)	4 (0.02)	11 (0.03)
Birth weight (g): n (%)				
Fetal macrosomia (≥4000g)	1,799 (3.4)	233 (3.2)	528 (3.3)	1,038 (3.5)
Normal (2500g – 3999g)	37,830 (71.6)	4,448 (61.6)	11,316 (70.6)	22,066 (74.7)
Low (1500g – 2499g)	9,759 (18.5)	1,681 (23.3)	3,042 (19.0)	5,036 (17.0)
Very Low (1000g – 1499g)	2,318 (4.4)	600 (8.3)	774 (4.8)	944 (3.2)
Extremely Low (<1000g)	926 (1.8)	251 (3.5)	330 (2.1)	345 (1.2)
Missing	179 (0.3)	10 (0.1)	40 (0.3)	129 (0.4)
Mean (SD)	2868 (729.2)	2684 (837.1)	2844 (743.6)	2926 (683.3)
Multiple pregnancy: n (%)	2,252 (4.3)	525 (7.3)	716 (4.5)	1,011 (3.4)
Missing	22 (0.04)	0 (0.0)	4 (0.02)	18 (0.06)
Died before 3 years of age (all-cause): n (%)	808 (1.5)	276 (3.8)	242 (1.5)	290 (1.0)
Age (months) at first infectious-cause hospitalisation				
≤6 days	1,354 (2.6)	360 (5.0)	447 (2.8)	547 (1.9)
7days – 27 days	2,418 (4.6)	442 (6.1)	870 (5.5)	1,106 (3.8)
28 days – 12 months	31,746 (60.4)	4,954 (68.7)	10,560 (66.2)	16,232 (55.2)
>12 – 24 months	12,171 (23.2)	1,201 (16.7)	3,158 (19.8)	7,812 (26.6)
>24 – 36 months	4,869 (9.3)	251 (3.5)	929 (5.8)	3,689 (12.6)
Exposure and infection status at time of hospital discharge: n (%)				
Children HEU	8,969 (17.0)	1,025 (14.2)	2,802 (17.5)	5,142 (17.4)
Children HUU	42,864 (81.2)	5,899 (81.7)	12,942 (80.7)	24,023 (81.3)
Children with HIV	978 (1.9)	299 (4.1)	286 (1.8)	393 (1.3)

Variable	Total N=52,811 (100%)	Pre-Option B+ (A) N=7,223 (13.7%)	Option B+ (B) N=16,030 (30.4%)	Universal ART (C) N=29,558 (56.0%)
MATERNAL CHARACTERISTICS				
Age (years) at delivery:				
Mean (SD)	27.2 (6.3)	27.2 (6.3)	27.1 (6.4)	27.2 (6.2)
Missing: n (%)	243 (0.5)	48 (0.7)	77 (0.5)	118 (0.4)
Maternal death by child age 3 years: n (%)	253 (0.5)	74 (1.0)	73 (0.5)	106 (0.4)
Maternal HIV first evidence among mothers with HIV (n=9,873)				
Before pregnancy	5,964 (60.4)	550 (42.3)	1,730 (56.3)	3,684 (67.0)
During pregnancy	3,370 (34.1)	552 (42.4)	1,163 (37.8)	1,655 (30.1)
Delivery/Postnatally	539 (5.5)	199 (15.3)	182 (5.9)	158 (2.9)
Maternal ART start among mothers with HIV (n=9,873)				
Before pregnancy	4,342 (44.0)	238 (18.3)	1,126 (36.6)	2,978 (54.2)
During pregnancy	3,520 (35.7)	262 (20.1)	1,304 (42.4)	1,954 (35.6)
Delivery/Postnatally	1,529 (15.5)	626 (48.1)	524 (17.0)	379 (6.7)
No evidence	482 (4.9)	175 (13.5)	121 (3.9)	186 (3.4)

Abbreviations – ART: antiretroviral therapy; CI: confidence interval; HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; LRTI: Lower respiratory tract infections; SD: standard deviation; TBM: Tuberculous meningitis; Pre-Option B+ (January 2008 – April 2013); Option B+ (May 2013 – August 2016); Universal ART (September 2016 – December 2021)

4.4.2. HIV-related characteristics of infants and mothers

Child HIV exposure and infection status:

At the time of hospital discharge, 17.0% of children were HEU, 81.2% HUU, and 1.9% CWH (Table 4.2). The certainty of classification of children HEU and HUU at time of hospitalisation was described in Chapter 3, Table 3.2. To recap, the combined HIV exposure and infection status of most children HEU was high (56.4%), but low for most children HUU (92.8%). The certainty of classification of the combined HIV exposure and infection status by period of hospital admission (Pre-Option B+/Option B+/Universal ART) is described in Appendix Table 4.2. The proportion of CWH among infectious disease admissions decreased from 7.0% in 2008 to 1.1% in 2021 (Figure 4.2 (1)). The proportion of children classified as HEU at hospital discharge increased from 14.1% in 2008 to 16.1% in 2021, with a peak of 18.3% in 2017. Children hospitalised with infectious diseases were less likely to have HIV, compared to being HEU, during the Option B+ (Relative Risk Ratio (RRR): 0.35; 95%CI: 0.29-0.42) and Universal ART (RRR: 0.26; 95%CI: 0.22-0.31) periods, relative to children admitted during the Pre-Option B+ period (Figure 4.2(2)).

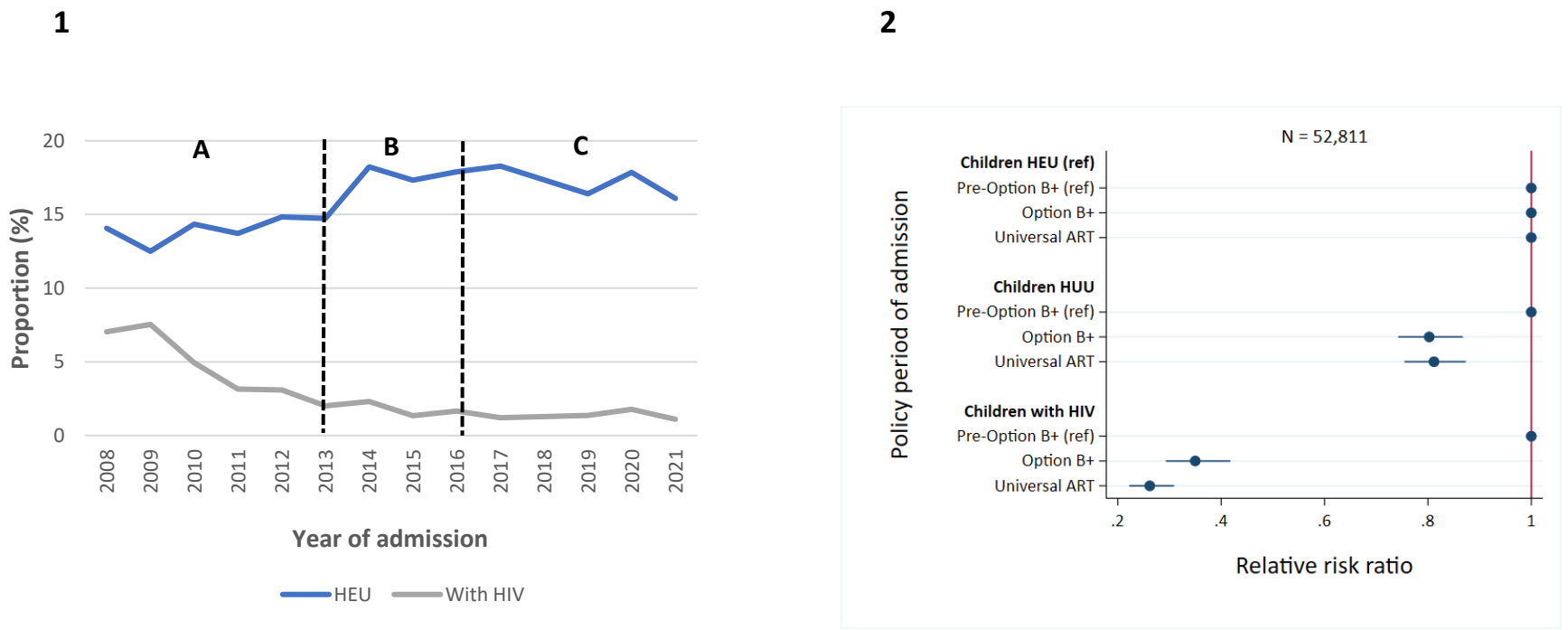


Figure 4.2: HIV exposure and infection status. (1) – Trends in HIV exposure and infection status among children HEU and CWH who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regressions assessing the association between child HIV exposure and infection status with policy period of hospital admission. N=52,811

Abbreviations – ART: antiretroviral therapy; CWH: children with HIV; HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; ref: reference group

Maternal HIV first evidence and ART start time:

Of CWH, 7.6% of mothers didn't have evidence of HIV (Appendix Table 4.3) and were excluded from further analyses of HIV-related characteristics. A descriptive summary of the proportion of mothers in respective maternal HIV first evidence and ART start categories is shown in Table 4.2. Among mothers of hospitalised children HEU and CWH, who were living with HIV, (N=9,873) the proportion with an HIV first evidence date before pregnancy increased from 20.2% in 2008 to 69.2% in 2021, with a peak of 75.2% in 2020 (Figure 4.3 (1)). Mothers were more likely to have an HIV first evidence date before pregnancy, versus during pregnancy, among children admitted during the Option B+ and Universal ART periods, compared to children admitted before the Option B+ period (Figure 4.3 (2)).

The proportion of mothers with HIV (N=9,873) starting ART before pregnancy increased from 5.8% in 2008 to 59.0% in 2021, peaking at 62.0% in 2020 (Figure 4.4 (1)), with mothers more likely to have started ART before pregnancy, versus at delivery/postnatally, among children admitted during the Option B+ and Universal ART periods, compared to children admitted before the Option B+ period (Figure 4.4 (2)).

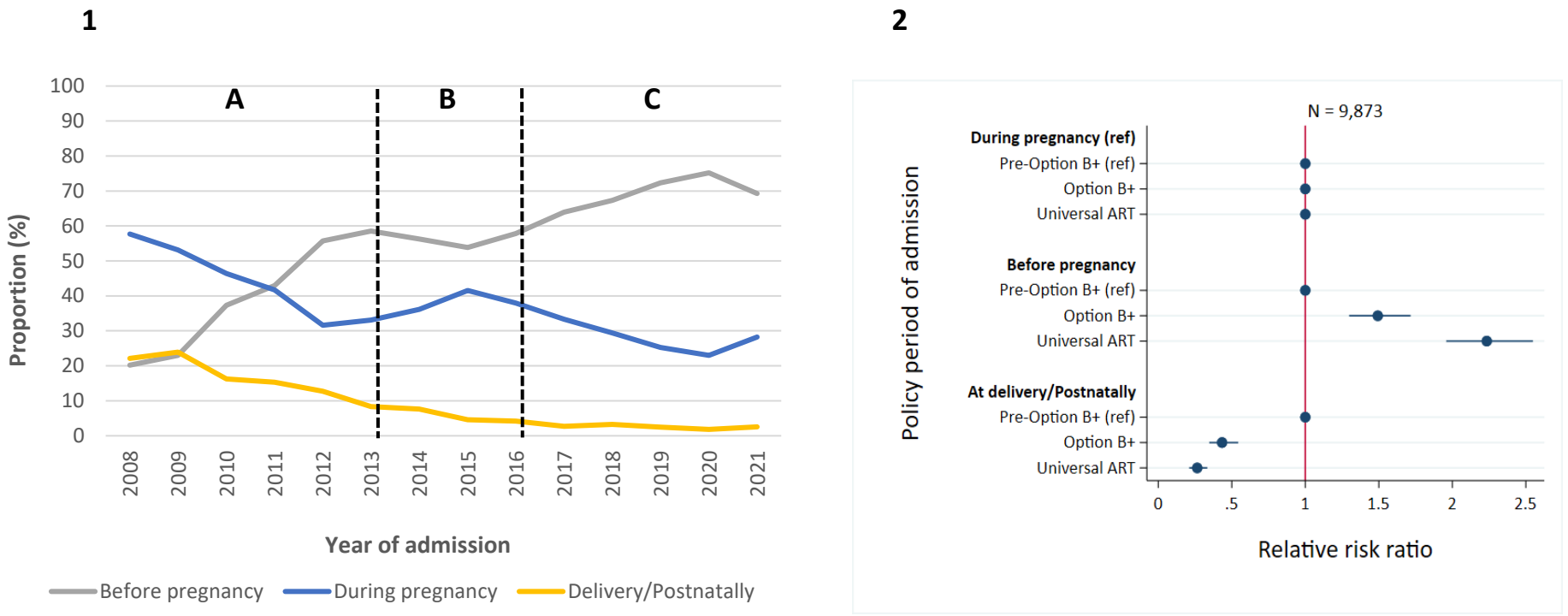


Figure 4.3: Timing of HIV diagnosis. (1) – Trends in timing of HIV diagnoses among mothers of children HEU and CWH, who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of mother HIV diagnosis (relative to pregnancy and delivery) with policy period of hospital admission. N=9,873.

Abbreviations – ART: Antiretroviral therapy; CWH: children with HIV; HEU: exposed to HIV and uninfected; ref: reference group

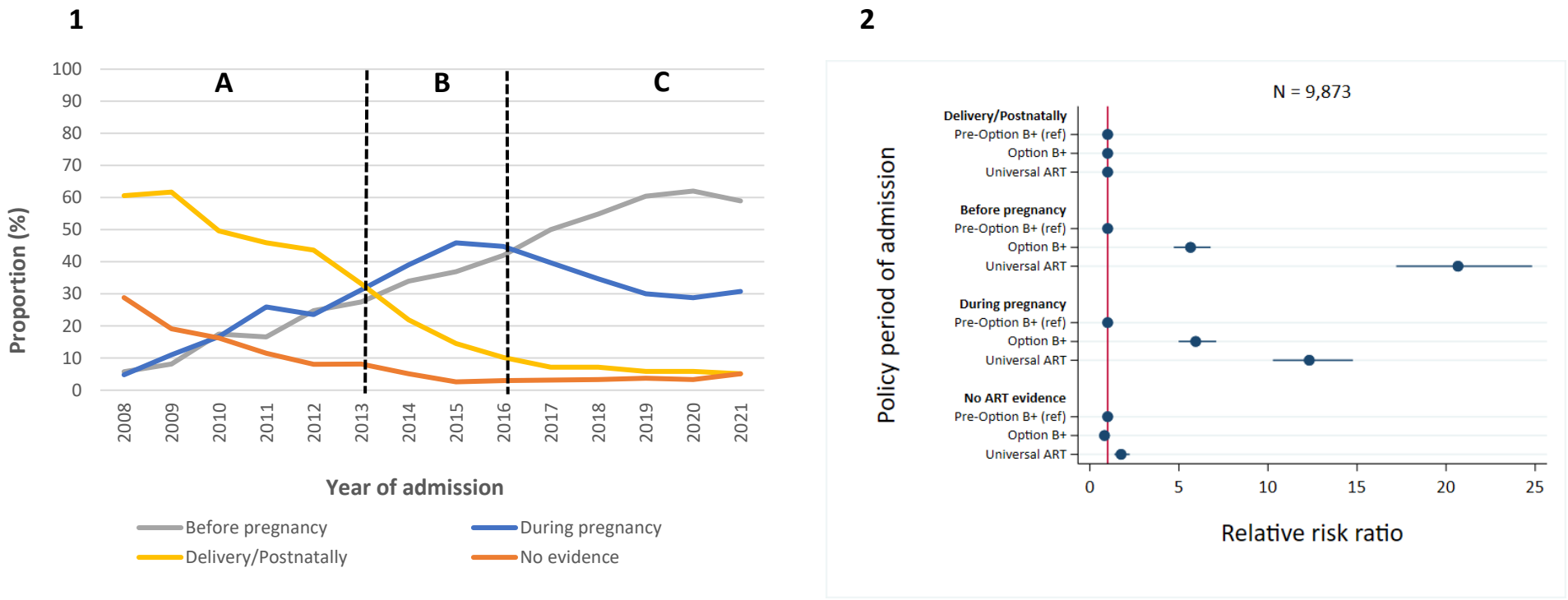


Figure 4.4: Timing of ART start. (1) – Trends in timing of ART start among mothers of children HEU and CWH who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of mother's ART start (relative to pregnancy and delivery) with policy period of hospital admission. N=9,873.

Abbreviations – ART: Antiretroviral therapy; CWH: children with HIV; HEU: exposed to HIV and uninfected; ref: reference

Child exposure to maternal ART:

The proportion of children exposed to HIV (HEU and CWH) who were exposed to maternal ART increased from 16.3% in 2008 to 87.2% in 2021 (Figure 4.5 (1)). The odds of having been exposed to maternal ART increased 8-fold (Odds Ratio: 8.41; 95% CI: 7.36-9.61) for children admitted to hospital during the Universal ART period compared to children admitted before the Option B+ period (Figure 4.5 (2)).

Among children exposed to maternal ART, the proportion exposed for the first time during late gestation/postnatally decreased from 58.8% in 2008 to 17.6% in 2021 (Figure 4.6 (1)). Children admitted to hospital with an infectious disease during the Option B+ and Universal ART periods were more likely to have first been exposed to maternal ART at conception, relative to late gestation/postnatally, compared with children admitted before the Option B+ period) (Figure 4.6 (2)).

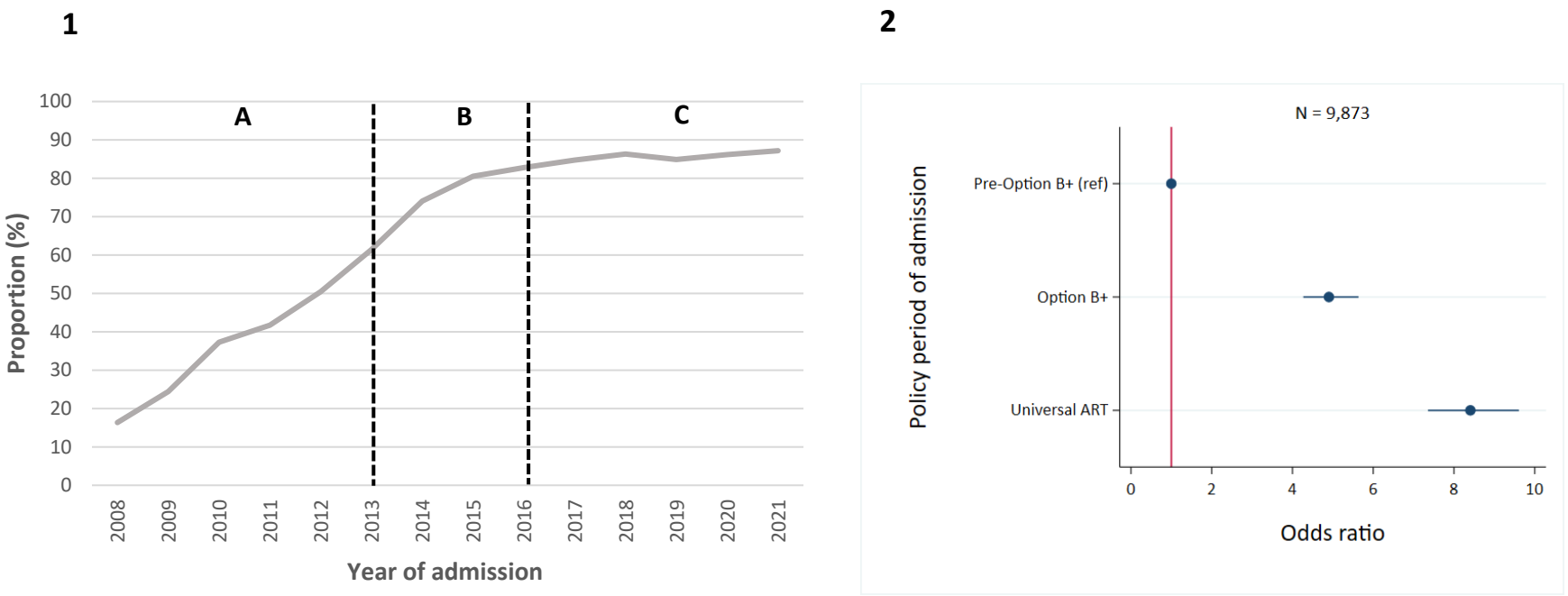


Figure 4.5: Child exposure to maternal ART. (1) – Trend in the proportion of hospital admittees HEU or with HIV who were exposed to maternal ART and hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the odds ratios (with 95% confidence intervals) from logistic regression assessing the association of infant exposure to maternal ART with policy period of hospital admission. N=9,873.

Abbreviations – ART: antiretroviral therapy; CWH: children with HIV; HEU: exposed to HIV and uninfected; ref: reference group

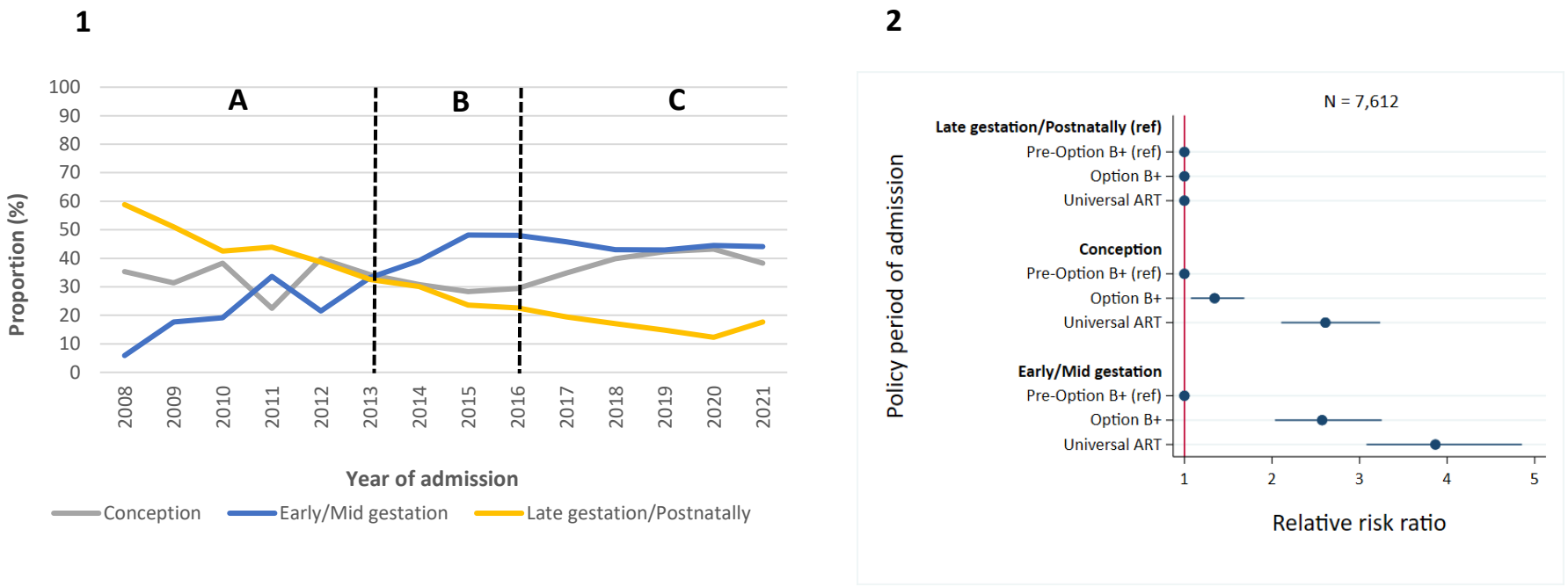


Figure 4.6: Timing of earliest child exposure to maternal ART. (1) – Trends in the proportion of hospital admittees' earliest exposure to maternal ART at different time points, among those who were exposed to maternal ART and hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of initial infant exposure to mother's ART start (relative to pregnancy and delivery) with policy period of hospital admission. N=7,612.

Abbreviations – ART: Antiretroviral therapy; mid: middle, ref: reference group

Maternal HIV viral load and CD4 count closest to delivery:

Among hospitalised children HEU with mothers who had viral load tests, >80% of mothers had viral loads <1000 copies/mL for all years except 2010 (72.7%) (Figure 4.7 (1)). Mothers of children HEU were more likely to have viral loads <1000 copies/mL (vs. ≥1000 copies/mL) for children admitted during the Universal ART period, compared to the period Pre-Option B+ (Figure 4.7 (2)). Among hospitalised CWH, the proportion of mothers with viral loads <1000 copies/mL peaked at 58.3% in 2009 and decreased to 25% in 2021(Figure 4.8(1)). Mothers of hospitalised CWH were less likely to have viral loads <1000 copies/mL (vs. ≥1000 copies/mL), for children admitted during the Option B+ period, compared to children admitted before the Option B+ period (Figure 4.8(2)).

Among hospitalised children HEU with mothers who had a CD4 count recorded, the proportion of mothers with CD4 count <350 cells/µL decreased from 90.6% in 2008 to 27.8% in 2021 (Figure 4.9 (1)). Mothers of hospitalised children HEU were more likely to have a CD4 count ≥500 cells/µL (vs. <350 cells/µL), for children admitted during the Option B+ (RRR: 3.54; 95% CI: 2.90-4.31) and Universal ART periods (RRR: 4.74; 95% CI: 3.92–5.73), compared to children admitted before the Option B+ period (Figure 4.9 (2)). Among hospitalised CWH, the proportion of mothers with a CD4 count <350 cells/µL was 70.8% in 2008 and 75.0% in 2021, with a minimum of 41.2% in 2020 (Figure 4.10 (1)). Mothers of hospitalised CWH were less likely to have a CD4 count ≥500 cells/µL (vs. <350 cells/µL), for children admitted during the Universal ART period (RRR: 0.61; 95% CI: 0.40–0.93), compared to children admitted before the Option B+ period (Figure 4.10 (2)).

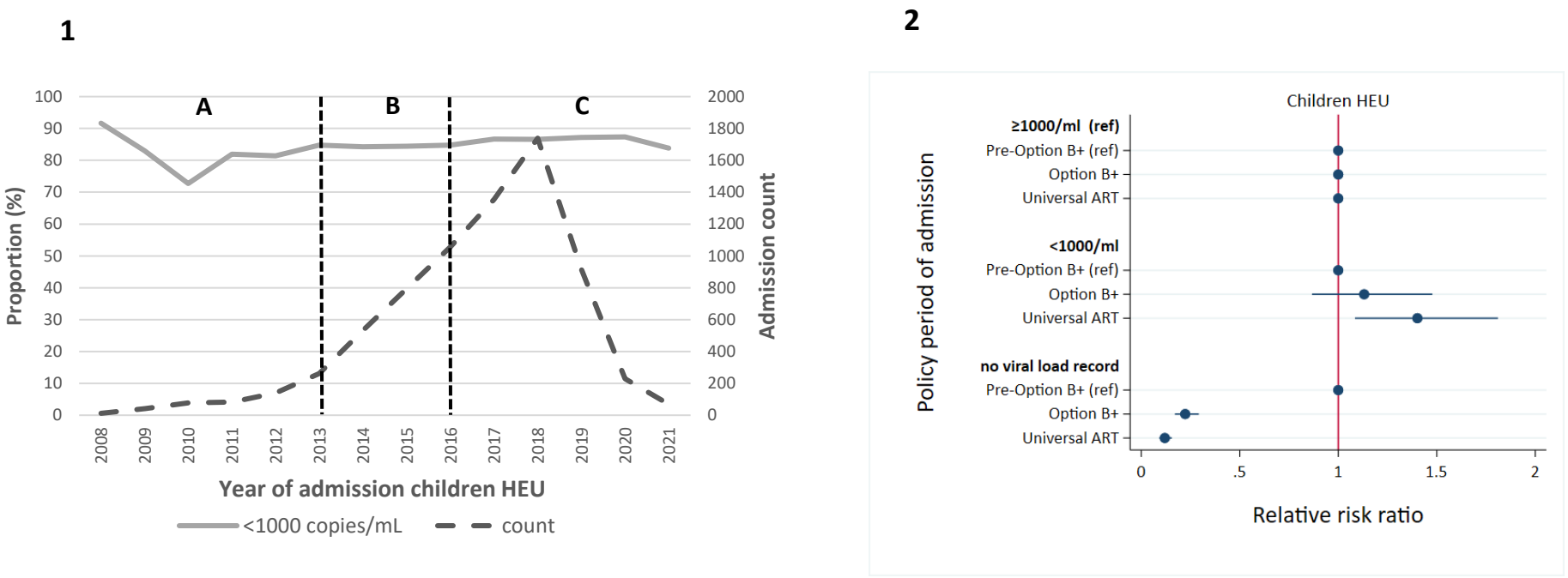


*Figure 4.7: Maternal viral load. (1) – Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis) hospital admittees HEU (N=7,306) whose mothers had a viral load of <1000 copies/mL within a year of delivery (including only mothers with a viral load record). The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of maternal viral load within a year of delivery with policy period of hospital admission, for children HEU (N=8,969). *I had no viral load record for 1,663 (18.5%) of mothers of children HEU.*

Abbreviations – ART: Antiretroviral therapy; CWH: Children with HIV; HEU: exposed to HIV and uninfected; ref: reference group

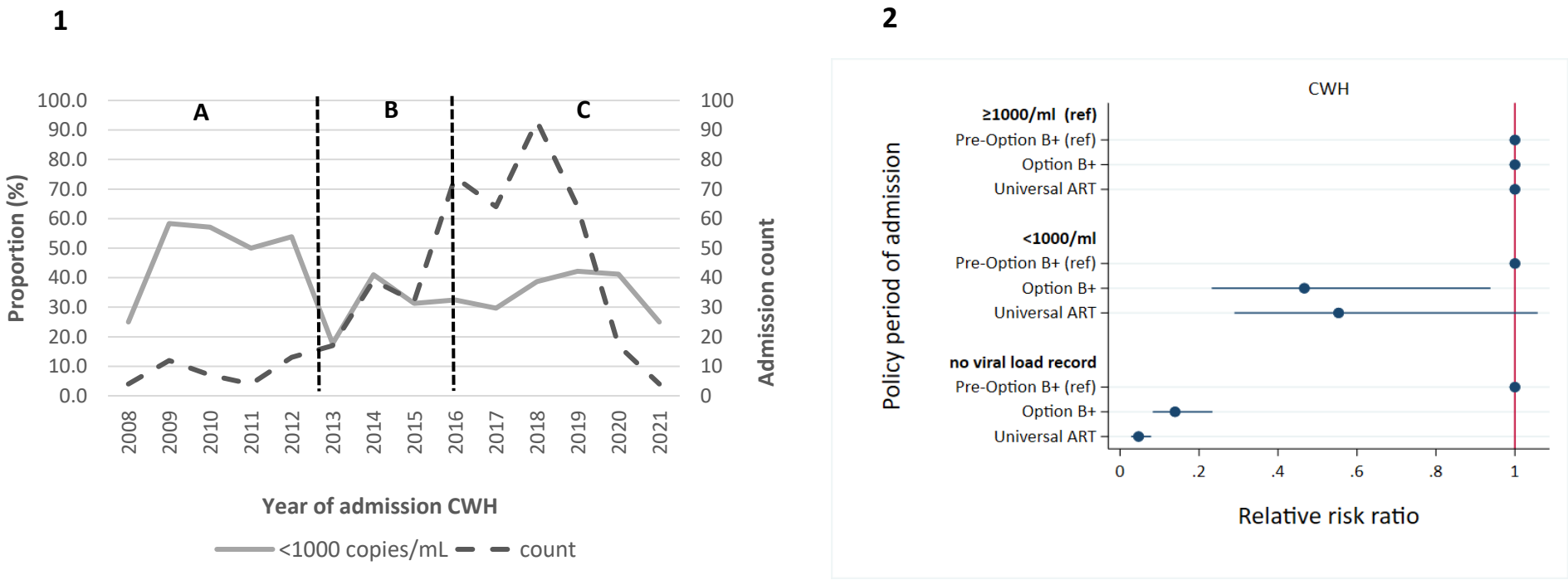


*Figure 4.8: Maternal viral load. (1) – Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis) hospital admittees with HIV (N=444) whose mothers had a viral load of <1000 copies/mL within a year of delivery (including only mothers with a viral load record). The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of maternal viral load within a year of delivery with policy period of hospital admission, for children CWH(N=904). *I had no viral load record for 460 (51.0%) of mothers of CWH.*

Abbreviations – ART: Antiretroviral therapy; CWH: Children with HIV; HEU: exposed to HIV and uninfected; ref: reference group

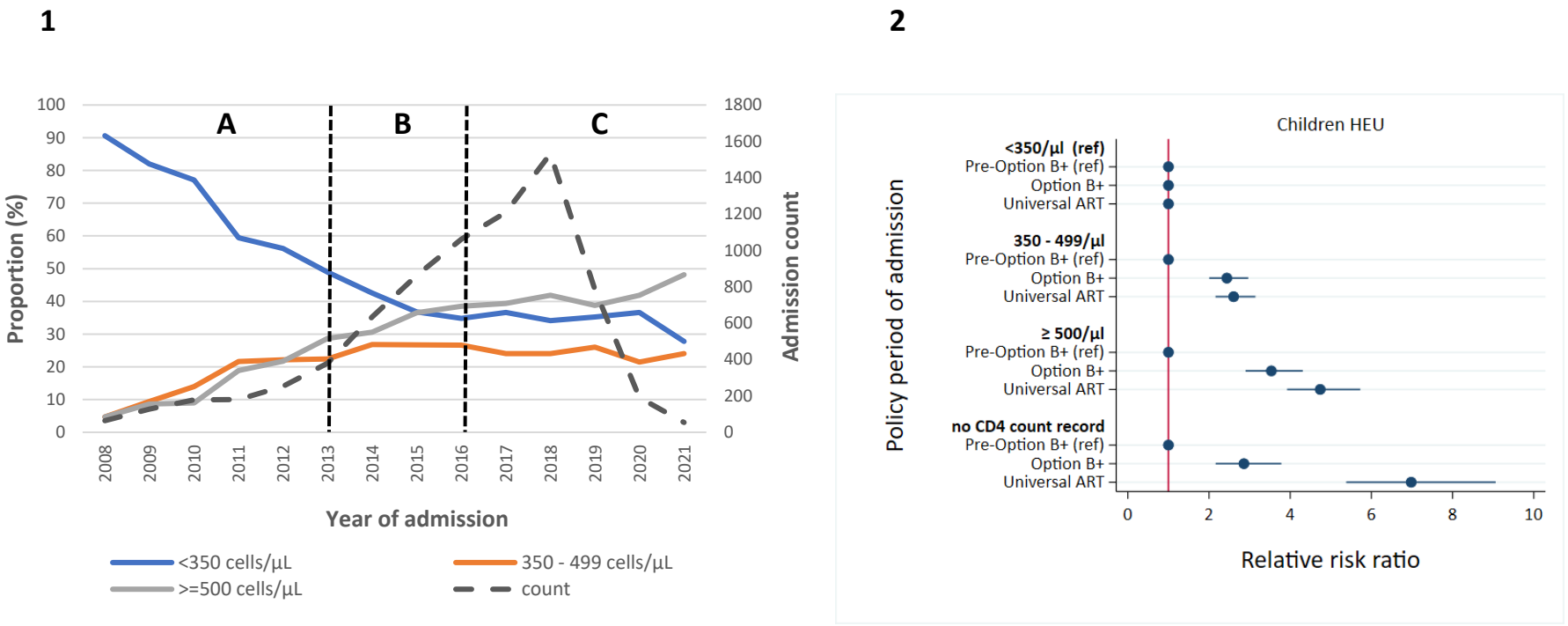


*Figure 4.9: Maternal CD4 count. (1) – Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis) hospital admittees HEU (N=7,523) whose mothers had CD4 count <350 cells/µL, 350 - 499 cells/µL, or ≥500 cells/µL within a year of delivery (including only mothers with a CD4 count record). The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of mother CD4 count within a year of delivery with policy period of hospital admission, for children HEU (N=8,969). *I had no CD4 count record for 1,456 (16.2%) of mothers of children HEU.*

Abbreviations – ART: Antiretroviral therapy; HEU: exposed to HIV and uninfected; ref: reference group

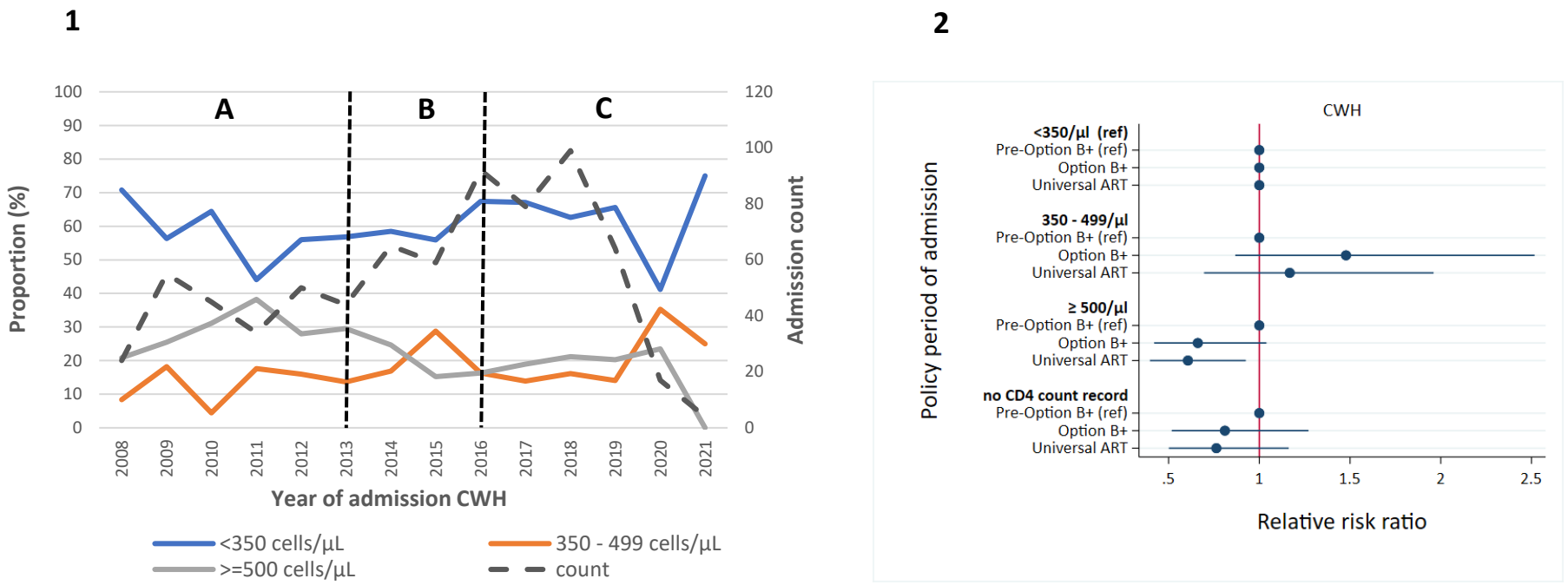


*Figure 4.10: Maternal CD4 count. (1) – Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis) hospital admittees with HIV (N=731) whose mothers had CD4 count <350 cells/µL, 350 - 499 cells/µL, or ≥500 cells/µL within a year of delivery (including only mothers with a CD4 count record). The vertical dotted lines demarcate different policy periods: A – Pre-Option B+, B – Option B+, C – Universal ART; (2) – Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of mother CD4 count within a year of delivery with policy period of hospital admission, for CWH (N=904) respectively. *I had no CD4 count record for 173 (19.1%) of mothers of children CWH.*

Abbreviations – ART: Antiretroviral therapy; CWH: Children with HIV; ref: reference group

4.5. Discussion

Since the scale-up of VTP for HIV in SA from 2002, tremendous gains have been made in preventing and treating paediatric HIV infection (166,179). My findings demonstrate how the HIV-related profile of children hospitalised for infectious diseases has changed from 2008 – 2021 in the WC, in the context of guideline amendments. Among hospitalised children, there was a decrease in the proportion of CWH and a corresponding increase in the proportion of children with mothers with evidence of HIV and starting ART before pregnancy. Consequently, more children were exposed to maternal ART during pregnancy. Furthermore, maternal health among hospitalised children improved during the study period with a substantial decrease in the proportion of mothers of children HEU who had a CD4 cell count <350 cells/µL.

During the scale-up of HIV VTP, the stabilisation of antenatal HIV prevalence and reduction in vertical HIV transmission resulted in a progressive decline in the CWH population and consequent increase in the prevalence of children HEU, since 2004 (179). Thembisa model (mathematical model of HIV epidemic in SA) estimates show a decrease in HIV prevalence, among children under age 3 years in the WC, from 1% in 2008 to 0.4% in 2021 (180). Furthermore, UNAIDS estimates of the national prevalence of children HEU (0-14 years) in SA increased from 12% in 2008 to 22% in 2018 (3). These patterns of decreasing prevalence of CWH and increasing prevalence of children HEU are reflected in my analysis. During the 14-year period under analysis, the proportion of CWH among infectious disease hospital admittees age ≤3 years dropped from 7% in 2008 to 1.3% in 2018. A study by Meyers *et al.* also showed a decreasing trend in the HIV prevalence among hospital admittees (0 – 14 years), although the HIV prevalence among hospital admittees that they reported for 2007 and 2010/11 (30% and 19%) was substantially higher than I observed in 2008 and 2010 respectively (176). The Meyers *et al.* study was conducted at a single large urban academic hospital in Gauteng province, which has a higher HIV prevalence among children than WC, and results may not be generalisable to my province-wide setting in the WC. The decrease in HIV prevalence observed in my cohort of hospitalised children corresponded with an increase in the prevalence of children HEU from 14% in 2008 to 17% in 2018. To my knowledge, this is the first study to report on the change in prevalence of children HEU among hospitalised

children over time. This increase in the proportion of children HEU, among hospitalised children, is comparable to the increasing prevalence of children HEU among the wider WC cohort (including non hospitalised children) that I analysed in Chapter 3.

The introduction of Option B+ has improved access to ART for all pregnant women living with HIV and dramatically reduced vertical HIV transmission (166). In the WC, between 2010 – 2013, Myer *et al.* observed a substantial increase in the proportion of pregnant women living with HIV entering antenatal care on ART, and initiating ART before delivery (181). They also reported a substantial reduction in delays to antenatal ART initiation after CD4 eligibility criteria were removed during the Option B+ period. In my analysis, mothers of children admitted to hospital in the Option B+ and Universal ART periods, compared to pre-Option B+, were significantly more likely to have evidence of HIV before pregnancy vs. during pregnancy and to have initiated ART before or during pregnancy vs. at delivery/postnatally. As a result, the proportion of children exposed to maternal ART increased over time, with children admitted during Universal ART vs. Pre-Option B+, having 8 times higher odds of maternal ART exposure. Furthermore, with mothers initiating ART earlier, children admitted in the later periods, compared to Pre-Option B+, were more likely to have been exposed to maternal ART for the first time at conception vs. late gestation/postnatally. The apparent slight increase from 2016 onwards in the proportion who had no ART evidence among mothers with HIV, may be due to better ascertainment of maternal HIV status in this period.

Throughout the study period, mothers of CWH at the time of infectious disease hospital admission predominantly had viral loads ≥1000 copies/mL near delivery, while the proportion of mothers of children HEU with viral loads <1000 copies/mL near delivery was >80% for all years except 2010. This is expected, given that the risk of vertical HIV transmission is increased with higher maternal viral load, particularly ≥1000 copies/mL (182,183).

As access to maternal ART improved over the years, and CD4 count was no longer recommended for monitoring persons living with HIV who are virally supressed on ART, the proportion of mothers of children HEU who had CD4 count recorded reduced, as did the proportion with CD4 <350 cells/µL near delivery, suggesting that maternal ART has not only reduced vertical HIV transmission, but also improved maternal health, as expected. The reduction in maternal deaths by the time of child age three years supports this finding. I found

that among CWH admittees, mothers predominantly had CD4 counts <350 cells/µL near delivery, corresponding with high viral loads observed in these mothers, suggesting that mothers not optimally sustaining ART in the context of a high coverage effective VTP programme, remain especially vulnerable.

Strengths and limitations

The WCPHDC provided a novel opportunity to assess, province-wide, the real-world trends in HIV-related characteristics of hospitalised children, using individual-level longitudinal health service data. In doing so, these analyses provided insight into the impact of the HIV VTP program in the WC over a 14 year period.

A limitation is that not all children were classified by HIV exposure and infection status with high certainty, particularly children HUU, of whom >90% were classified with low certainty (largely because rapid point-of-care HIV results are not routinely digitised). It is possible that some CWH may have been misclassified as HEU and children HEU as HUU. However, due to high rates of antenatal HIV testing within South Africa (>95%) (166), I am confident that most mothers living with HIV would have been identified during pregnancy, thereby limiting the misclassification of children exposed to HIV as unexposed. Additionally, of the children excluded from this analysis (N=1,370), 70% had mothers with a postnatal HIV first evidence date. I may therefore have a slight underestimation of children HEU or with HIV in my sample.

Another limitation of my findings is the accuracy and completeness of ICD-10 codes, particularly in the earlier years of the analysis. The classification of hospital admissions due to infectious causes relied on ICD-10 codes, which were previously shown to have poor reliability (184). However, in more recent years, the implementation of a standardised discharge summary has improved ICD-10 code completeness and accuracy (185), likely resulting in improved identification of infectious-cause hospitalisations. As a result, a large proportion of admissions included in my analyses were from 2015 onwards. Furthermore, it is probable that in the earlier years, admission codes were captured more accurately in tertiary hospitals and among more severely sick children. In the Pre-Option B+ period, >70% of admissions in my analyses were to tertiary hospitals (not shown), whereas >70% were to non-tertiary hospitals during the Universal ART period. It is possible that the Pre-Option B+ cohort is more representative of severely ill children than the cohorts of children admitted in the later

periods, potentially overestimating the prevalence of CWH, and other factors associated with severe disease, particularly low birth weight.

Given that there was a higher proportion of child and maternal in-hospital deaths, and CWH at the time of hospitalisation among children that were excluded from analyses compared to those included, it is likely that there was an underestimation of CWH in our sample.

I did not include children born out of province who relocated to and were hospitalised in the WC. I also only considered four infectious diseases that cause substantial morbidity and mortality in children. Other childhood infections, including pulmonary tuberculosis, were not included in this analysis. In children under age five, the diagnosis of tuberculosis is often based on clinical and radiographic features as bacteriological tests can be falsely negative. The algorithm to classify tuberculosis in children is therefore, not yet as well developed, as it is for the four infectious diseases included in this analysis, within the WCPHDC. My results may therefore not be generalisable to all child infectious diseases burdening the healthcare system.

Conclusions

Temporal trends among children hospitalised with infectious diseases highlight the positive impact of HIV VTP and increased ART access within SA. Whereas children of mothers with HIV were previously exposed to no or short duration maternal ART, in recent years the majority were exposed to maternal ART, frequently from early gestation. There were fewer CWH and a higher proportion of children HEU in recent years.

However, the finding that at least 1 in 6 children hospitalised in recent years were HEU, of which up to 87% were exposed to maternal ART, highlights the need to consider HIV and ART exposure status, and not just child HIV prevalence, when assessing the impact of the HIV epidemic on child health services. Further research is needed to quantify the burden of infectious diseases on the health system that is due to higher risk among children HEU relative to children HUU and whether there is a need for HEU-specific interventions in addition to interventions that improve the health and well-being of all children in resource limited settings.

CHAPTER 5. INFECTIOUS-CAUSE HOSPITALISATION IN CHILDREN HIV EXPOSED AND UNINFECTED AND CHILDREN HIV UNEXPOSED AND UNINFECTED

5.1. Chapter overview

Chapter 4 described temporal changes in HIV-related characteristics of children, born between 2013 and 2018, with infectious disease hospitalisations aged ≤3 years, across the WC province. I observed that, since 2008, among children hospitalised with infectious diseases, the proportion with HIV decreased while the proportion HEU and exposed to maternal ART from early pregnancy increased.

In this chapter, I assessed whether the rates of infection-related hospital admissions in those aged ≤3 years differ by HIV exposure status in a cohort of children born in the WC between 2013 and 2018 (a subset of the cohort born between 2008 and 2018). As this was a period during which mothers had increased access to maternal ART, specifically during pregnancy in the Option B+ period (starting in 2013) and then before pregnancy from the Universal ART period (from 2016), it was important to consider ART exposure in addition to HIV exposure. I therefore stratified children HEU by calendar time of maternal ART start relative to pregnancy start, and dispensing thereof, and analysed the difference in admission rates in these groups compared to children HUU. Furthermore, I described the causes of hospital admission in both groups of children and assessed factors associated with infectious disease hospital admissions in children HEU and HUU separately.

5.2. Introduction

As discussed in Chapter 1 (section 1.2.4), studies suggest that children HEU have higher risk of infectious morbidity than children HUU (7,9,10,12,17,24,97). Previous evidence particularly points to the greatest relative risk of hospital admission for children HEU vs. HUU being after

the first month of life but during the early infant-period up to six to 12 months of age, with similar high rates of admission, irrespective of HIV exposure, in the neonatal period. (9,24,76,96). Although the common causes of infectious morbidity (e.g. diarrhoea) are consistent across children HEU and HUU, studies suggest that these infections may be of greater severity in children HEU, leading to higher hospitalisation rates among this group (9,24,76). Admissions of greater severity would increase the burden on hospitals and hospital ICUs, especially in already resource-limited settings. In turn, this could lead to inadequate care at hospitals, which may have negative consequences for the wellness of all children (186,187). Research to better understand the health disparities in children HEU is a priority for HIV high-prevalence settings, not only to reduce the burden on healthcare services, but to ensure they survive and thrive in adolescence and adulthood (130).

Many of the studies comparing infectious disease outcomes in children HEU vs. HUU, that were discussed in Chapter 1, predate the Option B+ and especially the Universal ART access eras which started in 2013 and 2016 respectively in the WC. Since the implementation of Universal ART, all people with HIV have been able to access ART, thereby enabling women to start ART before pregnancy without having to meet CD4 count eligibility criteria (i.e. mothers starting ART before pregnancy prior to Universal ART would have to have been unwell or have had a previous pregnancy prior to Universal ART). These studies also predated the era of exclusive breastfeeding for 6 months with mixed feeding for an extended period (24 months). As highlighted in the section on challenges in this field of research (Chapter 1 – section 1.2.7), sample sizes of studies have been small and often restricted to a single healthcare facility, limiting the statistical power of studies to observe true differences between groups. Additionally, there is a need for routine-care linked maternal and child health data platforms, to help answer important child health related research questions and facilitate future evidence informed targeted interventions and policy changes (130).

In this chapter, I used province-wide data to describe the characteristics, causes, rates of, and factors associated with infectious disease hospital admissions ≤3 years of age in children born in the WC between 2013 and 2018 and determined whether these differ by HIV and ART exposure status.

5.3. Methods

5.3.1. Study design, data source and study setting

Details of the study design, data source and study setting have been described in Chapter 2 – sections 2.2 and 2.3.

5.3.2. Study participants

The inclusion and exclusion criteria for the analyses in this chapter are described in Chapter 2– section 2.4. I included all children with a recorded live birth in the WC between January 2013 and December 2018, as opposed to including children born between 2008 and 2018 as was done in Chapters 3 and 4. This time frame was chosen to focus the comparison of infection-related hospitalisation in children HEU vs. HUU to the Option B+ and Universal ART periods. Another key difference between this chapter and Chapter 4 is the inclusion of non-hospitalised children. The inclusion of both hospitalised and non-hospitalised children enabled the quantification of hospitalisation rates in children HEU vs. HUU. In Chapter 4, all children with a known positive HIV diagnosis at the time of hospitalisation were included; in this chapter only children with first HIV evidence after age 10 weeks were included and only if the timing of their HIV acquisition was known (i.e. they had a negative HIV test record prior to their HIV first evidence date). This was to allow their follow-up time as children HEU or HUU, before HIV acquisition, to be included in these analyses. Follow-up in these children was censored on the date of last HIV negative test. Children were excluded if they were known to have HIV at birth (up to age 10 weeks), or if their HIV first evidence date was after 10 weeks of age with an unknown time of HIV acquisition (i.e. they had no negative HIV test record), as this chapter focused on comparing hospitalisations in children HEU and HUU. As in all chapters of this thesis, children were excluded if: their mothers' HIV first evidence date was >10 weeks post-delivery; they were not electronically linked to their mothers; or they or their mothers had data inconsistencies. The number of children included and excluded for this chapter is shown in Figure 5.1. The key non-HIV related characteristics of those included in vs. excluded from these analyses were compared to assess potential selection bias in my sample (Appendix Table 5.1).

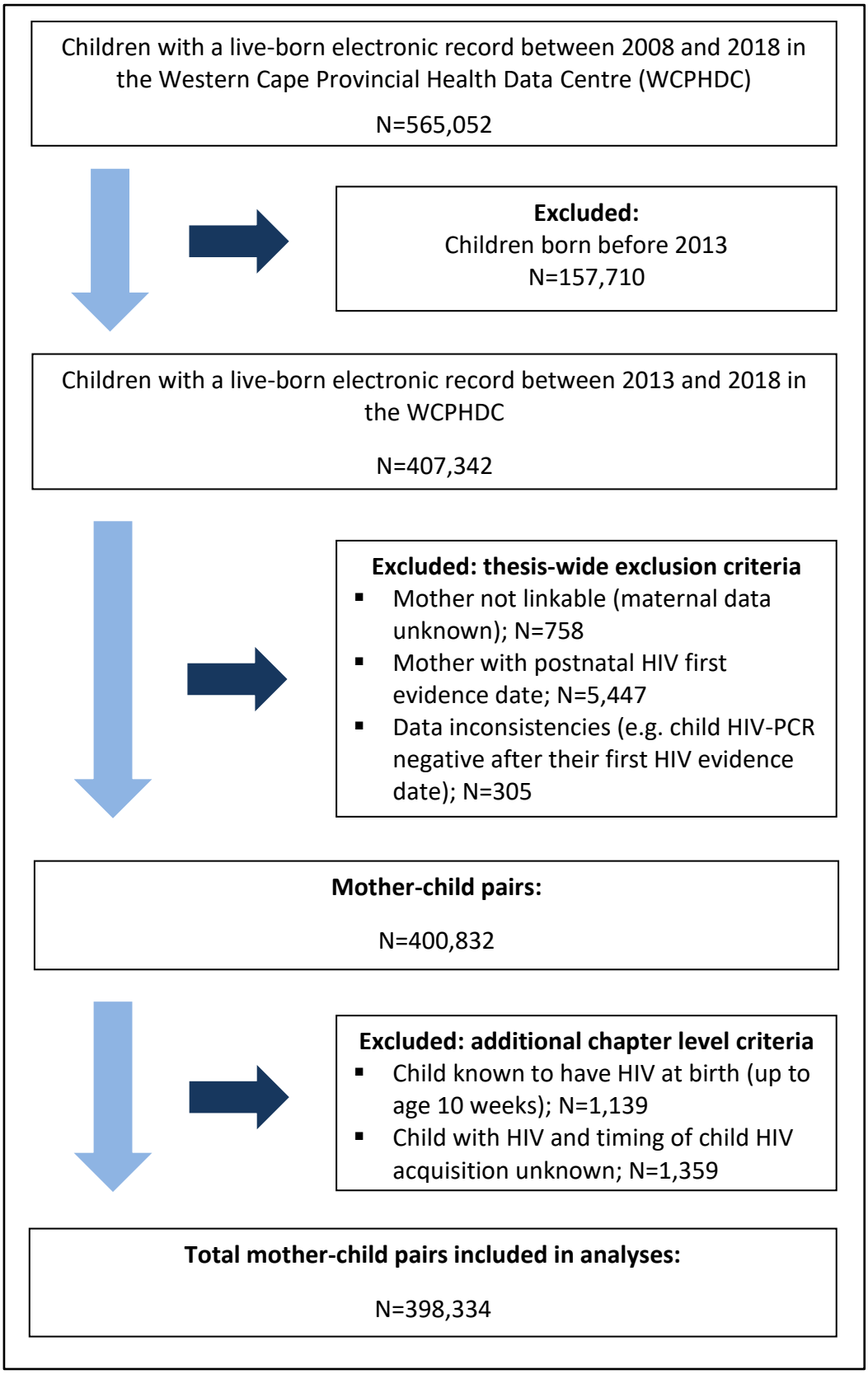


Figure 5.1: Flow diagram of mother-child pairs meeting the inclusion and exclusion criteria for analyses in Chapter 5

5.3.3. Procedures and measurements

The overarching data cleaning, management and extraction that I carried out for this chapter is described in Chapter 2– section 2.5. For this chapter, I used data from the WCPHDC on mother and child demographics (suburb of residence, maternal age, child sex), date of birth, birth weight, multiple pregnancy status and parity to define parameters used for mother and child descriptive statistics and the assessment of factors associated with infection-related hospitalisations. These parameters are defined in Chapter 2 – section 2.6. If the mother or child died in-facility during the study period (up to age three years), date of death was used for descriptive statistics and to determine follow-up time (for children). Mother and child laboratory test results (HIV PCR and ELISA) were used for classification of the certainty of child HIV exposure status and to calculate follow-up time if a child had evidence of having HIV. For children HEU, I used mother's HIV first evidence date, ART start and dispensing dates to define child HIV/ART exposure status. Maternal CD4 count and HIV viral load measurements/results were used to assess their association with infection-related admissions. For children with infectious disease hospital admissions[d], I used data on admission date, discharge date, causes of admission (i.e. LRTI, diarrhoea, meningitis, and TBM), admission facility type (e.g. Tertiary hospital /Regional hospital/District hospital), ICU admissions, and death during admission to describe hospitalisation characteristics.

Exposure

Children were classified as *in utero* HEU and HUU (regardless of certainty) at the start of follow-up (defined in Chapter 3 – section 3.3.3). As described in Chapter 3, I used simplified DECIPHER definitions to determine the certainty (high, moderate, low, no certainty) of *in utero* HIV exposure and infection status classifications at ages one and three years, and at time of hospitalisation for children who were hospitalised. For this chapter, I also used the same definitions to classify the certainty of *in utero* HIV exposure and infection status at the end of follow-up.

For regression models, I stratified children HEU by timing of maternal ART start and dispensing thereof relative to pregnancy start (approximated as 42 weeks before child date of birth, as

[d] Only hospitalisations for LRTI, diarrhoea, meningitis, and TBM in public sector facilities were included.

described in Section 2.6.1) and, for mothers who started ART before pregnancy, the start of Universal ART availability from 2016 onwards, as follows in Table 5.1:

Table 5.1: Definition criteria for the classification of HIV/ART exposure amongst children HEU

HIV/ART exposure group	Definition criteria[¥]
HEU – ART before pregnancy and ART start before Universal ART (<2016)	▪ Maternal ART started ≥42 weeks before child date of birth ▪ Mother was dispensed ART during first trimester (12 weeks of pregnancy) ▪ Maternal ART start date <2016
HEU – ART before pregnancy and ART start during Universal ART (≥2016)	▪ Maternal ART started ≥42 weeks before child date of birth ▪ Mother was dispensed ART during first trimester (12 weeks of pregnancy) ▪ Maternal ART start date ≥2016
HEU – ART restart during pregnancy	▪ Maternal ART started ≥42 weeks before child date of birth ▪ Mothers was dispensed ART during the second or third, but not first trimester of pregnancy
HEU – ART start during pregnancy	▪ Maternal ART start <42 weeks before child date of birth and before child date of birth ▪ Mother was dispensed ART during pregnancy
HEU – no ART during pregnancy	▪ Maternal ART start date at delivery or postpartum
HEU – unknown ART	▪ Maternal ART start before or during pregnancy ▪ No ART dispensing data during pregnancy
HEU – no ART evidence ever	▪ Mother did not have ART start date

Abbreviations – ART: antiretroviral therapy; HEU: HIV unexposed uninfected

[¥] - All criteria need to be met to be classified in respective categories

Outcomes

My primary outcome of interest was child's number of infectious disease hospital admissions for LRTI, diarrhoea, meningitis, or TBM, classified within the WCPHDC using ICD-10 codes as described in Chapter 2. For children with multiple infectious diagnoses for a single admission, the primary cause of admission was allocated in the order of: TBM, meningitis, LRTI, diarrhoea. I considered admissions to be of the same hospitalisation episode if they were within 21 days of the last discharge date.

Confounders

I considered maternal age (as defined in section 2.6.1) at child birth and socioeconomic status to be potential confounders, decided a priori using a directed acyclic graph (Figure 5.2). Suburb of residence was used as a proxy variable for socioeconomic status. As the suburb of residence variable consists of 125 suburbs, I divided these into Metropolitan and non-Metropolitan regions for descriptive purposes (Table 5.2).

Factors associated with infectious disease hospital admissions

Factors that I considered potentially associated with infection-related hospital admissions in all children were maternal age, child sex at birth, birth weight, multiple pregnancy status, parity and season of birth (Figure 5.2). These variables are defined in Chapter 2 – sections 2.6.1 and 2.6.2.

Among children HEU, I also considered maternal viral load (<1000 copies/mL, ≥1000 copies/mL) and maternal CD4 count (<350 cells/µL, ≥350 cells/µL) during pregnancy (using the first record within 42 weeks pre-delivery and 90 days post-delivery) as factors potentially associated with admissions.

These factors were selected based on data availability, literature, and a directed acyclic graph (Figure 5.2). It should be noted that, this directed acyclic graph includes additional factors the could not be included in the analyses; this will be discussed further in the thesis discussion (Chapter 7).

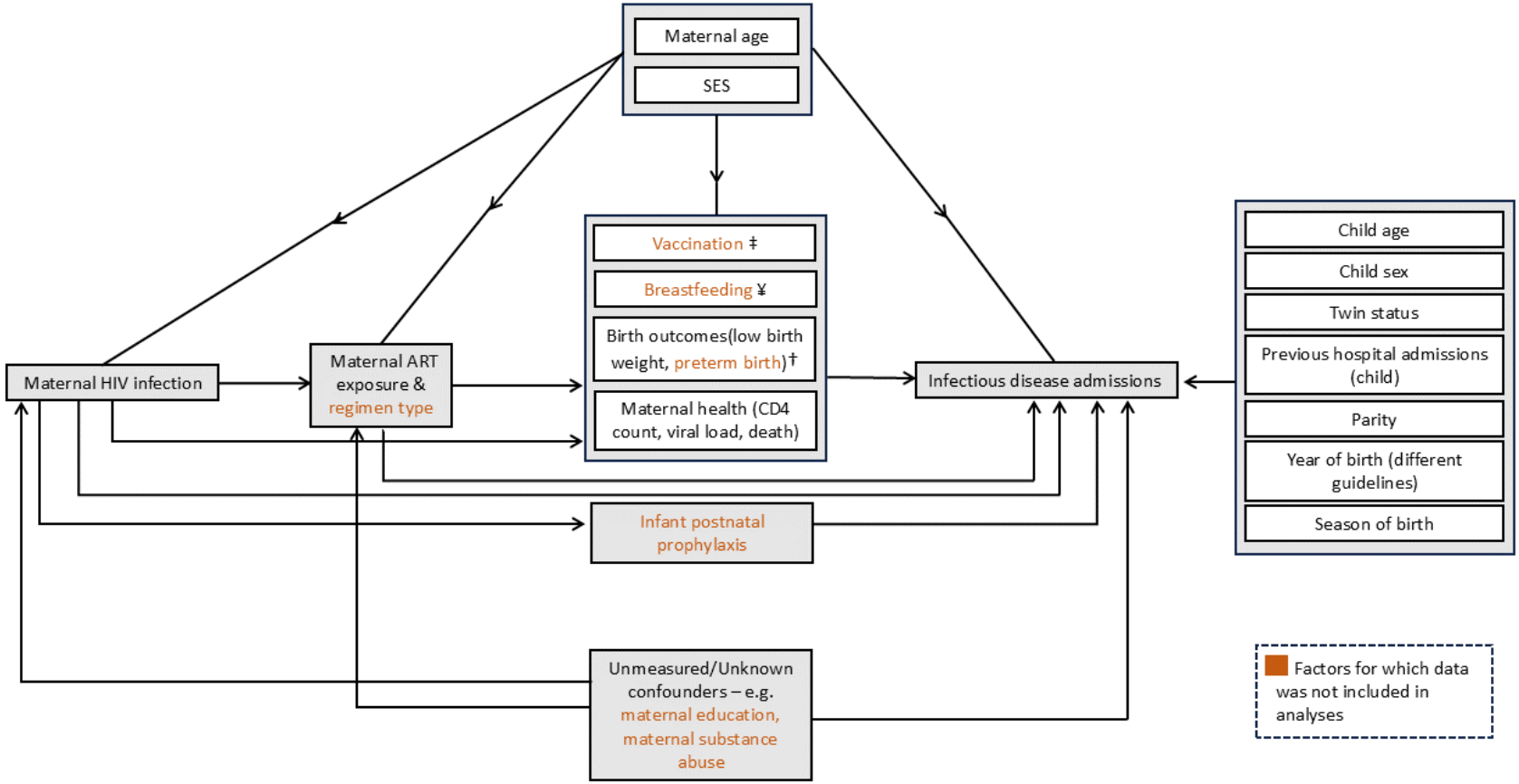


Figure 5.2: Directed acyclic graph representing the hypothesised relationships between maternal HIV infection, other factors, and infectious disease hospital admissions

[¥] Breastfeeding could act as a mediator between maternal HIV/ART and infectious disease admissions if mothers choose to or not to breastfeed because of their HIV/ART status. The beneficial effects of breastfeeding can however also be modified by HIV exposure (125,126).[†] Birth outcomes can only mediate the association between maternal ART exposure and infectious disease admission if mothers started ART before child date of birth. [‡] Vaccination could act as a mediator if maternal HIV/ART is associated with healthcare utilisation / vaccine uptake, but could also be an effect modifier of the maternal HIV/ART and infectious admission association. Abbreviations – ART: antiretroviral therapy; SES: socioeconomic status

5.3.4. Statistical analyses

I described key maternal, child and hospitalisation characteristics, by HIV exposure status, using proportions for categorical variables and means with standard deviations or medians with first and third quartiles for non-skewed and skewed continuous variables respectively. I used histograms to determine whether data were skewed or non-skewed. I compared maternal and child characteristics by HIV exposure status using the Chi-squared test for categorical variables and the two-sample t-test for continuous variables that were described using their mean. For hospitalisation characteristics I described year of hospitalisation, number of hospitalisations, age at earliest admission, and cause of admission. I also described length of stay, ICU admissions, deaths during admission, and the proportion of admissions that were at a tertiary hospital.

As previous literature reported that the relative risk of hospitalisation in children HEU vs. HUU changed with age (9,17), I estimated the association between HIV exposure status and infection-related hospitalisation within predefined age strata. Furthermore, to separate potential birth-related hospital admissions from those later in the neonatal period, I stratified neonatal admissions into early and late neonatal admissions (188,189). To describe the real-world association between HIV exposure and infection-related hospital admission, infectious disease hospitalisation incidence rates (admissions per 100 child years) among children HEU and HUU, regardless of timing of maternal ART start, were calculated and compared using crude incidence rate ratios (IRRs) for the following periods: age 0 – 3 years (36 months), early neonatal (age 0-6 days), late neonatal (age 7 – 27 days); postneonatal (age 28 days – 12 months), age >12 – 24 months, age >24 – 36 months.

I fitted mixed effects Poisson regression models with number of infectious disease admissions per child (admission count) as the outcome, accounting for varying person time at risk using an offset. Follow-up time was from date of birth until the earliest date of: last negative HIV test result if diagnosed with HIV, death, or age three years. Time spent in hospital following an infectious disease hospital admission was excluded

from follow-up time. All models included child-level (i.e. child identifier) random effects to account for the random variability in each child's rate of hospitalisation (i.e. overdispersion in the data) that isn't explained by the Poisson model. Models with and without the child-level random effect were compared using Akaike and Bayesian Information Criterion statistical measures and the best fit model (model with lowest Akaike and Bayesian Information Criterion) included child identifier as a random effect. In adjusted models containing suburb of residence, this was also included as a random effect to account for clustering within suburb and control for SES.

I first assessed the unadjusted association between each independent variable (exposure (HIV/ART) / potential confounders / factors potentially associated with the outcome) and admission count. In an attempt to get closer to the true causal estimate of the association between HIV/ART exposure and infectious disease admissions by addressing significant baseline differences between the exposure groups, I then evaluated the adjusted association between HIV/ART exposure and admission count, controlling for potential confounders (maternal age and suburb of residence). Maternal age and suburb of residence were the only variables that I considered as confounders as, based on the directed acyclic graph (Figure 5.2), they were associated with both the exposure and the outcome variable, but were not on the causal pathway between HIV/ART exposure and admission count.

Mediation is the indirect mechanism (one we want to understand) through which a cause can affect an outcome. Mediators are on the causal pathway between the exposure and the outcome and we therefore do not want to control for them when modelling (unless specifically interested in the direct mechanism). Conducting a mediation analysis can however help to better understand the mechanisms by which HIV/ART affects infectious disease outcomes amongst children. I did a sensitivity analysis to assess the potential mediating effect of birth weight on the association between HIV/ART exposure and admission count, by controlling for birth weight in addition to potential confounders (maternal age and suburb of residence). Potential future mediation analyses are discussed in the discussion section of this chapter (Section 5.5).

I also did a sensitivity analysis to assess the robustness of the adjusted association between HIV/ART exposure and admission count, controlling for maternal age and subdistrict, when including only children classified HEU or HUU with high or moderate certainty. Finally, using adjusted models, I assessed the association of selected factors with infectious disease hospital admissions when controlling for other factors of interest (listed under *Factors associated with infectious disease hospital admissions)*, among children HEU and HUU separately. To limit the number of model comparisons, I only present models for the neonatal (combining early and late neonatal admissions), postneonatal and >12 – 36-month periods. Analyses were done using Stata 17.0 (177).

5.4. Results

5.4.1. Child, mother and hospitalisation characteristics

407,342 children had a live-born electronic record in the WCPHDC between 2013 and 2018, of which 398,334 (97.8%) children were included for analyses in this chapter (Figure 5.1). As in Chapter 4, the proportion of child and maternal in-hospital deaths before child age 3 years was higher among children excluded vs. included in analyses (Appendix Table 5.1). Characteristics of included children and mothers are shown in Table 5.2. and Table 5.3. At the start of follow-up, 17.2% and 82.8% of children were classified as HEU and HUU respectively. By the end of follow-up, 413 children (372 HEU and 41 HUU) had been diagnosed with HIV and 123 children (105 HEU and 18 HUU) had unknown HIV status as their HIV first evidence date was after their third birthday. Among children HEU, 1.0%, 68.8%, and 13.8% were respectively classified with high, moderate, and low certainty of being HIV-uninfected at the end of follow-up, as shown in Appendix table 5.2. Among children HEU and HUU, 17.9% and 16.0% had a low birth weight (i.e. <2500g) and 3.6% and 2.6% were of a multiple pregnancy, respectively (Table 5.2).

Mothers of children HEU vs. HUU had a mean age at delivery of 29.8 (5.7) and 26.9 (6.2) years respectively (Table 5.2). Amongst HEU children born <2016 and ≥2016, 34.7% and 54.1% of mothers started ART before pregnancy, respectively (Table 5.3). Among mothers with data available, the median first CD4 count during pregnancy was

413 cells/µL (first quartile (Q1), third quartile (Q3): 274, 577) and 86.3% of mothers who were on ART at pregnancy start had viral load <1000 copies/mL nearest to pregnancy start.

Among children HEU and HUU, 11.5% and 10.9% had ≥1 infectious-cause hospitalisation between birth and age 3 years, respectively (

Table 5.4). Of these, 17.7% and 18.7% of children HEU and HUU had repeat admissions respectively. Of all admissions (first and repeat), children HEU vs. HUU had a median length of hospital stay of 3 (Q1,Q3: 2,6) vs. 2 (Q1,Q3: 1,4) days and a proportion of ICU admissions of 2.9% vs. 1.6%.

5.4.2. Causes of hospitalisation

Table 5.4 shows the distribution of the primary infectious cause of admissions, by HIV exposure status. For all admissions between birth and age 3 years, LRTI was the most common cause of admission, followed by diarrhoea, for children HEU and HUU.

Table 5.2: Characteristics of children (and their mothers), born in Western Cape from 2013 – 2018, by HIV exposure and infection status at the start of follow up (N=398,334)

Variable	Total N=398,334 (100.0%)	Children HEU N=68,455 (17.2%)	Children HUU N=329,879 (82.8%)	p-value
Child characteristics				
Sex: n (%)				
Male	201,533 (50.6)	34,608 (50.6)	166,925 (50.6)	0.130
Missing	784 (0.2)	156 (0.2)	628 (0.2)	
Birth weight (g): n (%)				
Foetal macrosomia(≥4000g)	16,545 (4.2)	2,308 (3.4)	14,237 (4.3)	<0.001
Normal (2500 – <4000)	315,714 (79.3)	53,714 (78.5)	262,000 (79.4)	
Low (1500 – <2500)	53,848 (13.5)	10,047 (14.7)	43,801 (13.3)	
Very Low (1500 – <2500g)	7,347 (1.8)	1,559 (2.3)	5,788 (1.8)	
Extremely Low (<1000g)	3,600 (0.9)	621 (0.9)	2,979 (0.9)	
Missing	1,280 (0.3)	206 (0.3)	1,074 (0.3)	
Mean (SD)	3,025 (635)	2,983 (637)	3,034 (633)	<0.001
Multiple pregnancy: n (%)				
Yes	11,045 (2.8)	2,474 (3.6)	8,571 (2.6)	<0.001
Missing	144 (0.04)	36 (0.05)	108 (0.03)	
Birth year: n (%)				
2013 & 2014	101,552 (25.5)	15,479 (22.6)	86,073 (26.1)	<0.001
2015 & 2016	135,710 (34.1)	23,141 (33.8)	112,569 (34.1)	
2017 & 2018	161,072 (40.4)	29,835 (43.6)	131,237 (39.8)	
Season of birth: n (%)				
Summer	97,698 (24.5)	16,970 (24.8)	80,728 (24.5)	0.174
Autumn	98,015 (24.6)	16,698 (24.4)	81,317 (24.7)	
Winter	100,519 (25.2)	17,170 (25.1)	83,349 (25.3)	
Spring	102,102 (25.6)	17,617 (25.7)	84,485 (25.6)	
Area of residence: n (%)				
Metropolitan	269,648 (67.7)	51,238 (74.8)	218,410 (66.2)	<0.001
Non-metropolitan	122,489 (30.8)	16,348 (24.9)	106,141 (32.2)	
Missing	6,197 (1.6)	869 (1.3)	5,328 (1.6)	
Died before 3 years of age (all-cause): n (%)				
Yes	4,547 (1.1)	866 (1.3)	3,681 (1.1)	0.001
HIV exposure and infection status at the end of follow-up: n (%)				
HEU	67,978 (17.1)	67,978 (99.3)	0 (0.0)	<0.001
HUU	329,820 (82.8)	0 (0.0)	329,820 (99.9)	
Children with HIV	413 (0.1)	372 (0.5)	41 (0.01)	
Unknown[¥]	123 (0.03)	105 (0.2)	18 (0.01)	
Maternal non-HIV-related characteristics				
Age at delivery (years): n (%)				
15 – 19	48,000 (12.1)	2,358 (3.4)	45,642 (13.8)	<0.001
20 – 39	337,437 (84.7)	63,431 (92.7)	274,006 (83.1)	
40 – 50	11,516 (2.9)	2,608 (3.8)	8908 (2.7)	
Missing: n (%)	1,381 (0.4)	58 (0.1)	1,323 (0.4)	
Mean (SD)	27.4 (6.2)	29.8 (5.7)	26.9 (6.2)	<0.001
Parity[†]: n (%)				
0	247,008 (62.0)	38,530 (56.3)	208,478 (63.2)	<0.001
1	106,047 (26.6)	20,718 (30.3)	85,329 (25.9)	
2	33,792 (8.5)	7,046 (10.3)	26,746 (8.1)	
≥3	11,426 (2.9)	2,149 (3.1)	9,277 (2.8)	
Missing: n (%)	61 (0.02)	12 (0.02)	49 (0.01)	
Maternal death by child age 3 years: n (%)				
Yes	1,207 (0.3)	631 (0.9)	576 (0.2)	<0.001

[¥] Unknown HIV exposure and infection status at end of follow-up are children whose HIV first evidence date was after age 3 years, but for whom date of acquisition is unknown

[†] Parity is recorded during current pregnancy and is based on digital evidence of prior pregnancies in the Western Cape only. True parity may therefore be underestimated.

Abbreviations – ART: antiretroviral therapy; g: grams, HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; SD: standard deviation

Table 5.3: Maternal HIV-related characteristics among children HEU born in Western Cape from 2013 - 2018

Variable	Children HEU N=68,455
Year of maternal ART start: n (%)	
<2013	15,359 (22.4)
2013 – 2015	30,162 (44.1)
≥2016	20,272 (29.6)
No ART evidence ever	2,662 (3.9)
Timing of first maternal ART evidence n (%)	
Among children born <2016 (N=26,574)	
Before pregnancy	9,220 (34.7)
During pregnancy	12,912 (48.6)
Delivery/Postpartum	3,348 (12.6)
No ART evidence ever	1,094 (4.1)
Among children born ≥2016 (N=41,881)	
Before pregnancy	22,648 (54.1)
During pregnancy	15,590 (37.2)
Delivery/Postpartum	2,075 (5.0)
No ART evidence ever	1,568 (3.7)
Maternal ART start and dispensing relative to pregnancy: n(%)	
ART before pregnancy and start before Universal ART (<2016)	19,600 (28.6)
ART before pregnancy and start during Universal ART (≥2016)	2,499 (3.7)
ART restart during pregnancy	6,140 (9.0)
ART start during pregnancy	27,581 (40.3)
No ART during pregnancy[‡]	6,339 (9.3)
Unknown ART[ϕ]	3,634 (5.3)
No ART evidence ever	2,662 (3.9)
First maternal viral load during pregnancy <1000 copies/mL: n(%)	
Among all women with HIV[☼] (N=56,744)	46,796 (82.5)
Among women on ART before pregnancy[☼] (N=21,943)	19,673 (89.7)
Among women not on ART before pregnancy[☼¶] *(N=33,485)*	26,076 (77.9)
No evidence*	11,711 (17.1)
First maternal CD4 count during pregnancy ≥350 copies/µL: n(%)	
Among all women with HIV[☼] (N=53,584)	32,951 (61.5)
Among women on ART before pregnancy[☼] (N=16,007)	11,829 (73.9)
Among women not on ART before pregnancy[☼¶] *(N=36,150)*	20,233 (55.6)
No evidence*	14,871 (21.7)
Median (Q1,Q3)	413 (274, 577)

[‡] Maternal ART start date at delivery or postpartum

[ϕ] Maternal ART start before or during pregnancy, but no electronic evidence of ART dispensing during pregnancy

[☼] Percentages are calculated as a proportion of those with a viral load or CD4 cell count measurement

[¶] Includes women who interrupted ART before pregnancy start and excludes women with no evidence of ART start

* Percentages are calculated as a proportion of all children HEU

Abbreviations – ART: antiretroviral therapy; HEU: exposed to HIV and uninfected; Q: quartile

Table 5.4: Hospitalisation characteristics of children who had at least 1 record of an infectious disease hospital admission, by HIV exposure status

Variable	Total	Children HEU	Children HUU
Total children in dataset	398,334	68,455	329,879
Total number of admissions	55,309	9,795	45,514
Children with ≥1 admission: n (%)	43,813 (11.0)	7,848 (11.5)	35,965 (10.9)
HOSPITALISATION CHARACTERISTICS PER CHILD	**N=43,813**	**N=7,848**	**N=35,965**
Admissions per child: n(%)			
1	35,683 (81.4)	6,455 (82.3)	29,228 (81.3)
2	6,001 (13.7)	1,056 (13.5)	4,945 (13.8)
3	1,398 (3.2)	222 (2.8)	1,176 (3.3)
≥4	731 (1.7)	115 (1.5)	616 (1.7)
Age at first admission: n(%)			
≤6 days	1,024 (2.3)	191 (2.4)	833 (2.3)
7days – 27 days	2,034 (4.6)	499 (6.4)	1,535 (4.3)
28 days – 12 months	26,370 (60.2)	5,012 (63.9)	21,358 (59.4)
>12 – 24 months	10,254 (23.4)	1,611 (20.5)	8,643 (24.0)
>24 – 36 months	4,131 (9.4)	535 (6.8)	3,596 (10)
Died during an infectious-cause admission: n (%)			
Yes	291 (0.7)	74 (0.9)	217 (0.6)
CHARACTERISTICS OF ALL ADMISSIONS – INCLUDING REPEAT ADMISSIONS	**N=55,309**	**N=9,795**	**N=45,514**
Year of hospitalisation: n(%)			
2013 – 2015	11,720 (21.2)	2,136 (21.8)	9,584 (21.1)
2016 – 2018	32,060 (58.0)	5,757 (58.8)	26,303 (57.8)
2019 – 2021	11,529 (20.8)	1,902 (19.4)	9,627 (21.2)
Admission diagnoses: n (%)[¥]			
LRTI	37,601 (68.0)	6,238 (63.7)	31,363 (68.9)
Diarrhoea	18,381 (33.2)	3,895 (39.8)	14,486 (31.8)
TBM	284 (0.5)	36 (0.4)	248 (0.5)
Meningitis	1,883 (3.4)	300 (3.1)	1,583 (3.5)
Length of hospital stay – days			
Median (Q1, Q3)	2 (1,4)	3 (2,6)	2 (1,4)
ICU admission: n (%)			
Yes	1,008 (1.8)	280 (2.9)	728 (1.6)
Hospitalisation at tertiary facility: n (%)			
Yes	16,045 (29.0)	2,992 (30.6)	13,053 (28.7)

[¥] Can be more than 1 admission diagnoses per hospitalisation. The denominator for each cause is total number of admissions in each exposure category.

Abbreviations – HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; ICU: Intensive care unit; LRTI: Lower respiratory tract infections; TBM: Tuberculous meningitis; Q: Quartile

5.4.3. Infectious disease hospitalisation rates and factors associated with admissions

Crude hospitalisation incidence rates among children HEU and HUU (regardless of maternal ART):

Table 5.5 reports the crude hospitalisation incidence rates among children HEU and HUU, regardless of timing of maternal ART start. The overall rate of infectious-cause hospitalisation was 4% higher in children HEU vs. HUU (incidence rate ratio (IRR=1.04; 95% CI:1.02-1.07)). Admission rates were highest during the early neonatal period vs. later periods and similar for both children HEU (14.6/100 child years) and HUU (13.3/100 child years). The relative difference in admission rates for children HEU vs. HUU was highest during the late neonatal period (IRR=1.57; 95% CI: 1.42-1.74). This difference began to taper between 28 days and age 1 year of life. After 1 year of age, HEU children had a lower rate of admission than HUU children (12 months – 24 months IRR=0.92; 95% CI: 0.88-0.96; 24 months – 30 months IRR =0.73; 95% CI 0.68-0.80).

Table 5.5: Infectious-cause hospitalisations comparing children HEU and children HUU – crude incidence rates and incidence rate ratios per age interval

Age category	All children	Children HEU	Children HUU	Crude IRR (95% CI)
Overall				
Number of children at risk	398,334	68,455	329,879	–
Number of admissions	55,309	9,795	45,514	–
Person-time (years)	1178,524	201,508	977,016	–
Incidence per 100 child years	4.69	4.86	4.66	1.04 (1.02 – 1.07)
0 – 6 days				
Number of children at risk	398,334	68,455	329,879	–
Number of admissions	1,024	191	833	–
Person-time (years)	7,590	1,305	6,285	–
Incidence per 100 child years	13.49	14.64	13.25	1.10 (0.94 – 1.29)
7 – 27 days				
Number of children at risk	395,236	67,922	327,314	–
Number of admissions	2,034	499	1,535	–
Person-time (years)	22,636	3,886	18,750	–
Incidence per 100 child years	8.99	12.84	8.19	1.57 (1.42 – 1.74)
28 days – 12 months				
Number of children at risk	395,170	67,901	327,269	–
Number of admissions	30,883	5,887	24,996	–
Person-time (years)	362,637	62,026	300,610	–
Incidence per 100 child years	8.52	9.49	8.03	1.14 (1.11 – 1.17)
>12 months – 24 months				
Number of children at risk	393,731	67,315	326,416	–
Number of admissions	14,832	2,358	12,474	–
Person-time (years)	392,629	67,111	325,518	–
Incidence per 100 child years	3.78	3.51	3.82	0.92 (0.88 – 0.96)
>24 months – 36 months				
Number of children at risk	393,476	67,244	326,232	–
Number of admissions	6536	860	5676	–
Person-time (years)	393,032	67,180	325,852	–
Incidence per 100 child years	1.66	1.28	1.74	0.73 (0.68 – 0.80)

Abbreviations – HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; IRR: Incidence rate ratio

Unadjusted associations between maternal HIV/ART exposure and infectious-cause hospitalisations:

When stratifying children HEU by timing of maternal ART start, unadjusted analysis showed that during the neonatal period infectious-cause hospitalisation was 27-50% higher in all groups of children HEU vs. HUU, irrespective of maternal ART status (Table 5.6A). Although attenuated, the rate of hospitalisation during the postneonatal period was still higher for all groups of children HEU whose mothers have a record of ART, compared to children HUU. There was a substantial reduction in the relative rate of hospitalisation, from the neonatal (uIRR=1.41; 95% CI: 1.24-1.60) to the postneonatal period (uIRR=1.06; 95% CI: 1.01-1.11), among children HEU whose mothers started ART during pregnancy, compared to those HUU. During the >12 months – 36 months age period, children HEU whose mothers started ART either before or during pregnancy or compared to children HUU, had a reduced rate of hospitalisation.

Adjusted associations between maternal HIV/ART exposure and infectious-cause hospitalisations:

After adjusting for the potential confounders of, maternal age and subdistrict of residence, the crude IRRs that were >1 for the association between HIV exposure (stratified by maternal ART start) and infectious-cause hospitalisation increased slightly during the postneonatal period, e.g. for children HEU whose mothers started ART before pregnancy and Universal ART, vs. children HUU, the IRR increased from uIRR=1.18; 95% CI: 1.11-1.24 to aIRR=1.30; 95% CI: 1.22-1.38 when controlling for maternal age and subdistrict of residence (Table 5.6A). During the >12 months – 36 months period, crude IRRs for these associations that were <1 attenuated towards and/or increased beyond the null after adjusting for potential confounders. In the same age group (12 – 36 months), children HEU, compared to HUU, whose mothers started ART during pregnancy, still had a reduced rate of hospitalisation after adjusting for potential confounders (aIRR=0.91; 95% CI:0.85-0.97). There was a small amount of variability at a suburb level that was not accounted for by the models (e.g., the variance of the suburb random effect for the 12 – 36 month model in Table 5.6 A = 0.24; 95% CI: 0.17-0.33). The variability at an individual level within suburbs was, however, more

substantial than the variability between suburbs (e.g., the variance of the individual level random effect (within suburbs) for the 12 – 36 month model in Table 5.6 A = 2.24; 95% CI: 2.16-2.32).

When incorporating birth weight (as a potential mediator) into the model, in addition to maternal age and subdistrict, the association between HIV/ART exposure and infectious-cause hospitalisation among children HEU whose mothers were not on ART during pregnancy (HEU – no ART during pregnancy), compared to children HUU, decreased slightly, but remained >1 during the neonatal (aIRR=1.40; 95% CI:1.10-1.79) and postneonatal (aIRR=1.30; 95% CI:1.19-1.44) periods (Appendix Table 5.3).

Sensitivity analysis including only children classified HEU or HUU with high or moderate certainty:

When restricting to children HEU and HUU classified with moderate or high certainty, the estimates for the adjusted association between HIV/ART exposure and infectious-cause hospitalisation were substantially higher than in the main analysis for children HEU whose mothers were not on ART during pregnancy (HEU – no ART), compared to children HUU, for all three age groups; e.g. during the neonatal period, the aIRR for children HEU whose mothers were not on ART during pregnancy, compared to children HUU, was aIRR=1.89; 95% CI:1.35-2.64 when restricting to children HEU and HUU classified with moderate or high certainty, compared to aIRR=1.49; 95% CI:1.17-1.90 when including children classified with low certainty (Table 5.6B). Compared to other HEU groups, children HEU whose mothers started ART before pregnancy and during Universal ART, vs. children HUU, had the lowest increased rate of hospitalisation during the neonatal and postneonatal period. During the >12 – 36-month period, there was some weak evidence that they had a reduced rate of hospitalisation, compared to children HUU (aIRR=0.80; 95% CI:0.63-1.02).

Table 5.6: Mixed effects Poisson regression models assessing the association between HIV/ART exposure and infectious-cause hospitalisation in HIV uninfected children within different age groups. Both unadjusted incidence rate ratios (uIRRs) and adjusted (aIRRs) are shown, where adjustment was for maternal age at delivery and suburb of residence. (A) Models include children classified HEU and HUU with high, moderate or low certainty; (B) Models are restricted to children classified HEU or HUU with high or moderate certainty.

	(A) Low, moderate and high certainty children HEU and HUU (N=398,334)					
Age group	**Neonatal (days 0 – 27)**		**Postneonatal (28 days – 12 months)**		**(>12 months – 36 months)**	
	uIRR (95%CI)	**aIRR (95%CI) (N=390,779)[¥]**	**uIRR (95%CI)**	**aIRR (95%CI) (N=387,722)**	**uIRR (95%CI)**	**aIRR (95%CI) (N=386,314)**
HIV/ART exposure						
HUU	Ref	Ref	Ref	Ref	Ref	Ref
HEU – ART before pregnancy and start before Universal ART(<2016)	1.38 (1.1-1.60)	1.40 (1.21-1.63)	1.18 (1.11-1.24)	1.30 (1.22-1.38)	0.90 (0.83-0.97)	1.10 (1.02-1.19)
HEU – ART before pregnancy and start during Universal ART (≥2016)	1.34 (0.90-2.00)	1.35 (0.90-2.02)	1.17 (1.00-1.38)	1.23 (1.05-1.44)	0.79 (0.63-0.98)	0.91 (0.73-1.14)
HEU – ART restart during pregnancy	1.50 (1.17-1.91)	1.54 (1.21-1.98)	1.34 (1.22-1.47)	1.45 (1.32-1.60)	0.94 (0.82-1.07)	1.09 (0.96-1.25)
HEU – ART start during pregnancy	1.41 (1.24-1.60)	1.44 (1.27-1.63)	1.06 (1.01-1.11)	1.13 (1.08-1.19)	0.78 (0.73-0.83)	0.91 (0.85-0.97)
HEU – no ART during pregnancy[†]	1.48 (1.16-1.89)	1.49 (1.17-1.90)	1.38 (1.28-1.51)	1.44 (1.31-1.58)	0.98 (0.87-1.11)	1.11 (0.98-1.26)
HEU – unknown ART[‡]	1.27 (0.90-1.79)	1.31 (0.93-1.85)	1.23 (1.08-1.39)	1.29 (1.14-1.47)	0.89 (0.75-1.06)	1.00 (0.84-1.18)
HEU – no ART evidence ever	1.41 (0.97-2.07)	1.41 (0.97-2.07)	0.92 (0.78-1.09)	0.96 (0.81-1.13)	0.78 (0.64-0.97)	0.85 (0.69-1.05)
Maternal age at delivery (years)						
15 – 19	Ref	Ref	Ref	Ref	Ref	Ref
20 – 39	0.84 (0.57-1.22)	0.89 (0.80-0.99)	0.80 (0.69-0.93)	0.89 (0.85-0.92)	0.83 (0.68-1.03)	0.91 (0.86-0.95)
40 – 50	1.00 (0.60-1.67)	0.76 (0.59-0.97)	0.89 (0.72 – 1.09)	0.89 (0.82-0.97)	1.14 (0.87-1.51)	0.93 (0.84-1.03)
Variance of random effect (95% CI): Suburb	–	0.06 (0.03-0.10)	–	0.16 (0.11-0.22)	–	0.24 (0.17-0.33)
Variance of random effect (95% CI): Suburb > Study ID	–	–	–	1.74 (1.69-1.80)	–	2.24 (2.16-2.32)

	(B) Moderate and high certainty children HEU and HUU (N=62,220)					
Age group	Neonatal (days 0 – 27)		Postneonatal (28 days – 12 months)		(>12 months – 36 months)	
	All children uIRR (95%CI)	**All children aIRR (95%CI) (N=59,233)**	**All children uIRR (95%CI)**	**All children aIRR (95%CI) (N=59,092)**	**All children uIRR (95%CI)**	**All children aIRR (95%CI) (N=58,930)**
HIV/ART exposure						
HUU	Ref	Ref	Ref	Ref	Ref	Ref
HEU – ART before pregnancy and start before Universal ART(<2016)	1.47 (1.14-1.90)	1.46 (1.13-1.90)	1.29 (1.18-1.41)	1.36 (1.24-1.49)	0.93 (0.84-1.04)	1.03 (0.91-1.16)
HEU – ART before pregnancy and start during Universal ART (≥2016)	1.23 (0.74-2.04)	1.24 (0.75-2.07)	1.19 (1.00-1.41)	1.20 (1.01-1.43)	0.76 (0.60-0.96)	0.80 (0.63-1.02)
HEU – ART restart during pregnancy	1.56 (1.11-2.20)	1.59 (1.12-2.24)	1.47 (1.31-1.66)	1.54 (1.37-1.74)	0.99 (0.85-1.16)	1.06 (0.90-1.25)
HEU – ART start during pregnancy	1.50 (1.17-1.91)	1.50 (1.18-1.93)	1.23 (1.14-1.34)	1.26 (1.15-1.38)	0.88 (0.80-0.98)	0.94 (0.84-1.05)
HEU – no ART during pregnancy†	1.87 (1.34-2.62)	1.89 (1.35-2.64)	1.78 (1.58-2.00)	1.79 (1.58-2.01)	1.23 (1.05-1.43)	1.27 (1.08-1.49)
HEU – unknown ART‡	1.39 (0.88-2.20)	1.42 (0.90-2.25)	1.54 (1.33-1.79)	1.59 (1.37-1.86)	1.09 (0.89-1.33)	1.13 (0.92-1.39)
HEU – no ART evidence ever	1.60 (0.92-2.75)	1.61 (0.93-2.78)	1.26 (1.03-1.54)	1.25 (1.01-1.53)	1.02 (0.78-1.32)	1.04 (0.79-1.36)
Maternal age at delivery (years)						
15 – 19	Ref	Ref	Ref	Ref	Ref	Ref
20 – 39	0.97 (0.68-1.38)	0.87 (0.61-1.24)	0.88 (0.78-0.99)	0.83 (0.73-0.94)	0.92 (0.78-1.09)	0.98 (0.83-1.16)
40 – 50	1.05 (0.63-1.75)	0.90 (0.53-1.53)	0.89 (0.74-1.07)	0.84 (0.70 -1.02)	1.10 (0.87-1.40)	1.18 (0.93-1.51)
Variance of random effect (95% CI): Suburb	–	<0.001 (0.00-0.00)	–	0.11 (0.06-0.16)	–	0.18 (0.11-0.28)
Variance of random effect (95% CI): Suburb > Study ID	–	–	–	1.40 (1.30-1.52)	–	2.03 (1.87-2.21)

¥As it was not possible to have a repeat admission during the neonatal period, child identifier was not included as a random effect in the neonatal period model.

†Maternal ART start date at delivery or postpartum

‡Maternal ART start before or during pregnancy, but no electronic evidence of ART dispensing during pregnancy

Abbreviations – aIRR: adjusted incidence rate ratio; ART: Antiretroviral therapy; CI: Confidence interval; HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; uIRR: unadjusted incidence rate ratio

Factors associated with infectious-cause hospitalisation:

When evaluating potential factors associated with infectious-cause hospitalisation in children HEU and HUU separately, older maternal age (20 – 39 and 40 – 50 years for children HUU; 20 – 39 years for children HEU) was associated with decreased rates of hospitalisation across all hospitalisation age periods, among children HEU and HUU, in unadjusted (Appendix Table 5.4) and adjusted (Table 5.7) analyses. Factors associated with increased rates of hospitalisation in unadjusted and adjusted analyses, among both children HEU and HUU, were: male sex (all hospitalisation age periods), low/very low/ extremely low birth weight (all hospitalisation age periods), multiple pregnancy status (postneonatal period), parity 2/≥3 (neonatal period for children HEU and postneonatal period for children HEU and HUU), and being born in autumn (neonatal and postneonatal hospitalisation periods). Among children HEU, maternal HIV viral load ≥1000 copies/mL during pregnancy (postneonatal hospitalisation period) was associated with increased rates of hospitalisation in unadjusted and adjusted analyses.

Table 5.7: Adjusted Poisson regression models assessing factors associated with infectious-cause hospitalisation in children without HIV within different age groups

Age group	Neonatal[¥] (days 0 – 27)		Postneonatal (28 days – 12 months)		(>12 months – 36 months)	
	Children HUU aIRR (95%CI) (N=321,544)	**Children HEU aIRR (95%CI) (N=67,150)**	**Children HUU aIRR (95%CI) (N=319,070)**	**Children HEU aIRR (95%CI) (N=66,618)**	**Children HUU aIRR (95%CI) (N=318,245)**	**Children HEU aIRR (95%CI) (N=66,046)**
Maternal age at delivery (years)						
15 – 19	Ref	Ref	Ref	Ref	Ref	Ref
20 – 39	0.87 (0.77-0.98)	0.79 (0.53-1.15)	0.83 (0.79-0.86)	0.81 (0.70-0.94)	0.88 (0.84-0.92)	0.87 (0.70-1.08)
40 – 50	0.61 (0.44-0.83)	0.90 (0.53-1.51)	0.76 (0.69-0.84)	0.89 (0.73-1.10)	0.80 (0.71-0.91)	1.20 (0.91-1.59)
Child sex: male	1.24 (1.14-1.34)	1.29 (1.11-1.50)	1.41 (1.37-1.45)	1.45 (1.36-1.54)	1.25 (1.21-1.29)	1.27 (1.17-1.38)
Birth weight (g)						
Normal (2500 – <4000)	Ref	Ref	Ref	Ref	Ref	Ref
Fœtal Macrosomia (≥4000)	1.20 (0.99-1.46)	1.22 (0.83-1.80)	0.82 (0.75-0.88)	0.90 (0.76-1.08)	0.96 (0.88-1.05)	0.87 (0.68-1.11)
Low (1500 – <2500)	1.51 (1.35-1.68)	1.23 (1.00-1.52)	1.61 (1.55-1.68)	1.62 (1.50-1.75)	1.38 (1.32-1.45)	1.29 (1.15-1.44)
Very low (1000 <1500)	2.68 (2.16-3.33)	2.28 (1.58-3.30)	3.88 (3.59-4.19)	3.10 (2.67-3.59)	2.21 (1.98-2.47)	1.92 (1.52-2.42)
Extremely low (<1000)	3.33 (2.44-4.54)	2.64 (1.41-4.96)	5.17 (4.59-5.83)	4.26 (3.29-5.51)	3.44 (2.92-4.06)	2.72 (1.82-4.05)
Multiple pregnancy	0.83 (0.65-1.07)	0.91 (0.61-1.36)	1.38 (1.27-1.49)	1.27 (1.10-1.45)	0.87 (0.77-0.97)	1.09 (0.88-1.35)
Parity						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.04 (0.95-1.15)	1.07 (0.90-1.28)	1.14 (1.10-1.18)	1.12 (1.05-1.20)	1.09 (1.04-1.13)	1.08 (0.98-1.18)
2	1.01 (0.86-1.17)	1.30 (1.02-1.65)	1.23 (1.17-1.30)	1.10 (0.99-1.21)	1.15 (1.08-1.23)	1.10 (0.97-1.27)
≥3	1.13 (0.90-1.42)	1.59 (1.10-2.29)	1.21 (1.11-1.31)	1.30 (1.11-1.52)	0.95 (0.85-1.07)	0.95 (0.74-1.23)
Season of birth						
Summer	Ref	Ref	Ref	Ref	Ref	Ref
Autumn	1.53 (1.37-1.72)	1.36 (1.10-1.67)	1.06 (1.02-1.11)	1.05 (0.97-1.14)	1.01 (0.96-1.06)	0.87 (0.77-0.98)
Winter	1.26 (1.12-1.42)	1.00 (0.80-1.24)	0.82 (0.79-0.86)	0.92 (0.85-1.00)	0.97 (0.92-1.02)	0.89 (0.80-1.00)
Spring	0.96 (0.84-1.08)	0.87 (0.70-1.09)	0.81 (0.78-0.84)	0.86 (0.79-0.93)	0.98 (0.94-1.03)	0.92 (0.82-1.03)
CD4 count during pregnancy						
≥350 cells/µL	–	Ref	–	Ref	–	Ref
<350 cells/µL	–	0.96 (0.81-1.15)	–	1.07 (0.99-1.14)	–	0.99 (0.90-1.09)
No CD4 record	–	0.95 (0.77-1.16)	–	1.05 (0.97-1.14)	–	1.03 (0.93-1.15)
Viral load during pregnancy						
<1000 copies/mL	–	Ref	–	Ref	–	Ref
≥1000 copies/mL	–	1.17 (0.94-1.42)	–	1.17 (1.08-1.27)	–	1.05 (0.94-1.18)
No VL record	–	0.99 (0.80 -1.23)	–	1.04 (0.96-1.13)	–	0.93 (0.82-1.04)

Age group	Neonatal[¥] (days 0 – 27)		Postneonatal (28 days – 12 months)		(>12 months – 36 months)	
Variance of random effect (95% CI): Suburb	0.06 (0.03 – 0.11)	0.02 (0.002-0.30)	0.15 (0.11-0.21)	0.12 (0.08-0.20)	0.22 (0.16-0.31)	0.22 (0.14-0.34)
Variance of random effect (95% CI): Suburb > Study ID	_	_	1.58 (1.52-1.65)	1.47 (1.35-1.59)	2.16 (2.08-2.24)	2.29 (2.10-2.50)

Models were adjusted for year of child birth.

[¥]As it was not possible to have a repeat admission during the neonatal period, child identifier was not included as a random effect in the neonatal period models.

Abbreviations – aIRR: adjusted incidence rate ratio; ART: antiretroviral therapy; CI: confidence interval; g: grams, HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; SD: standard deviation

5.5. Discussion

In this provincial birth cohort, there were higher rates of infectious disease hospitalisation in the first year of life in children HEU compared to HUU, regardless of timing of maternal ART start. After the first year of life, HIV exposure was not associated with an increased risk of hospitalisation. Among children whose mothers started ART either before pregnancy and during Universal ART or during pregnancy, some analyses even indicated a reduced risk of hospital admission relative to HUU after the first year of life.

LRTIs were the most common cause of hospitalisation in children HEU and HUU. Factors associated with higher rates of hospitalisation in children HEU and HUU were male sex, low birth weight, multiple pregnancy status, higher parity, being born in Autumn, and maternal HIV viral load ≥1000 copies/mL during pregnancy (children HEU). Older maternal age at delivery was protective against hospitalisation for children HEU and HUU.

My finding of increased risk of infectious disease admissions in children HEU vs. HUU in the first year of life supports what single-facility studies in the WC have reported (17,23,24). I observed the greatest relative rate of admission among children HEU, compared to HUU, to be during the late neonatal period (7 – 27 days of life). Similarly, another study in the WC reported a higher incidence of infection-related hospitalisations among children HEU between 8 days and 3 months of life (17). These results are however contrary to that of systematic review of studies from sub-Saharan Africa and a recent study from WC showing no evidence for a difference in admission rates by HIV exposure status in the neonatal period (9,96). This may be due to past studies being underpowered to assess the narrow neonatal period.

When stratifying children HEU by maternal ART start, the increased risk of admission was substantially higher for children HEU whose mothers started ART before pregnancy, restarted ART during pregnancy, or were not on ART during pregnancy, compared to those HUU. Although there is an observed reduction in the association between HIV exposure and infectious disease admissions from the neonatal to the postneonatal period, the greatest reduction is among children HEU whose mothers started ART during pregnancy. This points to

the potential of maternal ART to ameliorate the excess risk of infectious diseases in the postneonatal period among children HEU vs. HUU. Mothers starting ART during pregnancy is also an indication that they were engaged in antenatal care at some point during pregnancy. Engagement in antenatal care has been reported to be linked to better engagement in postnatal paediatric care (168,190), and this could potentially play an important role in reducing excess morbidity among HEU children. This finding is contrary to a European study that found that maternal ART start before pregnancy reduced the excess risk of infection-related hospitalisation in children HEU compared to HUU, but when mothers initiated ART during pregnancy this excess risk was increased (97).

Although unexpected, there are a number of possibilities for why the excess risk of hospitalisation may be lower for children HEU whose mothers started ART during pregnancy than for those whose mothers started ART before pregnancy, relative to children HUU. As discussed above, it's certain that mothers initiating ART during pregnancy would have had some antenatal care, but the extent to which mothers on ART before pregnancy engaged in antenatal care is unknown. Additionally, mothers who started ART before pregnancy may have been living with HIV for longer and started ART prior to Universal ART, when they had to meet disease severity guidelines to access ART (i.e. they had a very poor immune status when initiating ART). However, when stratifying mothers starting ART before pregnancy into the pre and post Universal ART period (2016), the increased risk of hospitalisation remained similar for both groups of children HEU, compared to HUU, during the postneonatal period. Furthermore, Slogrove *et al.* observed in a 2018/2019 WCPHDC cohort, that ART start pre-conception was associated with low and very low birth weight, compared to ART start early in pregnancy (116). It is therefore important to consider the possible impact of antiretroviral exposure at conception. Nonetheless, the high increased risk of hospitalisation during the neonatal and postneonatal period in children HEU whose mothers restarted ART during pregnancy or weren't on ART during pregnancy, relative to children HUU, highlights the importance of initiating and sustaining ART.

After age 12 months I found evidence that the risk of infection-related hospital admission was reduced for children HEU whose mothers initiated ART before pregnancy and during Universal ART (in some models) and those whose mothers initiated ART during pregnancy, relative to children HUU. Other studies have reported that the increased risk of infection-related

hospitalisation in children HEU wanes with age, with Le Roux *et al.* reporting the association between HIV exposure and infection-related admissions after 12 months as (aIRR=0.71; 95% CI:0.23-2.16) (9,17), but to my knowledge, no studies have stratified HIV exposure by timing of maternal ART start. One hypothesis is that maternal ART before or during pregnancy, in the context of Universal ART, could be a proxy for better maternal health and/or engagement in healthcare services and once the effects of being exposed to HIV and ART wane after the first year of life the benefits of better engagement in healthcare are seen with these groups having lower risk of hospital admission. Further studies are necessary to assess this. Another consideration is that pulmonary tuberculosis was not included as an infectious event outcome in my study. A SA study by Moore *et al.* showed that pulmonary tuberculosis accounts for the highest fraction of pneumonias in children HIV-exposed aged 1-5 years, compared to eighth highest among children HIV-unexposed (191). In the first year of life pulmonary tuberculosis was ranked second for both groups of children. It may therefore be possible that the HIV/ART associations with infection-related hospitalisations observed for the 12 – 36 month age period are under estimated. There is also potential survival/follow-up bias reducing the associations for the 12 -36 month period as a higher proportion of children HEU compared to HUU died in-facility during follow-up, and I did not have data on out of facility deaths. Additionally, as children diagnosed with HIV were removed from the HEU group at the time of their last negative test, the most vulnerable children HEU (i.e. those with characteristics associated with vertical transmission such as maternal high viral load) are excluded progressively over time.

When I conducted a sensitivity analysis excluding all children with a low certainty HIV exposure and infection status classification, there was an increase in the estimated relative risk of admission among children HEU in all ART groups except for those whose mothers started ART before pregnancy and during Universal ART, compared to children HUU. The increased risk was particularly high for children HEU whose mothers were not on ART during pregnancy. Higher certainty of HIV exposure amongst this group of children may be associated with being admitted to hospital, as children, and sometimes mothers, are tested for HIV during hospital admission. Furthermore, as I did not have access to point-of-care mother HIV testing results, there may have been misclassification of children HEU as HUU low certainty. This would have reduced the association between HIV/ART exposure and hospital admission.

Although I assessed the potential affect of birthweight as a mediator between HIV/ART exposure and infectious disease hospitalisation, further in-depth mediation analyses are required to understand this potential indirect pathway between exposure and outcome. Counterfactual-based mediation methods are the preferred option as they solve the limitations of traditional methods (135). Using counterfactual-based mediation it will be possible to determine the natural indirect effect of the exposure on the outcome and from there calculate the "proportion mediated" (for each mediator) which represents the extent to which the effect of HIV/ART exposure on infectious admissions operates through each mediator. Other potential mediators which could be investigated, if data is available, include preterm birth, breastfeeding, and maternal health.

As reported by other studies, LRTIs and diarrhoea were the predominant primary causes of hospitalisation in this research cohort (17,23,24), both of which are known major causes of morbidity and mortality death among young children (192). Furthermore, the proportion of admissions due to diarrhoea was higher amongst children HEU compared to HUU. Diarrhoea is complexly linked to infant breastfeeding practices, making it difficult to distinguish the role of suboptimal breastfeeding and HIV exposure as risk factors for morbidity (9). Mortality and morbidity due to LRTIs and diarrhoea can be substantially reduced through optimal breastfeeding and childhood vaccinations; strategies already recommended in current guidelines and requiring no major new advances in technology (192). Nevertheless, even children HEU that are exclusively breastfed are at increased risk of infectious disease outcomes compared to children HUU (193).

Older maternal age was associated with a reduced risk of hospitalisation in children HEU and HUU. Because the mean maternal age was younger for children HUU compared to HEU, the unadjusted estimates for the association between HIV/ART were potentially underestimated. When I controlled for maternal age as a potential confounder I, therefore, found that the aIRR estimates increased away from one during the postnatal period and that the estimates that were <1 for the >12 month – 1 year period increased towards one or beyond 1. In this study, higher parity was associated with an increased risk of infection related admission among children HEU and HUU. As a higher proportion of mothers of children HEU had a parity of 1 / 2 / ≥3 compared to children HUU, it is possible that parity was driving part of the observed increased risk of hospitalisation in children HEU vs. HUU. Evidence suggests that parity could

be acting as a proxy for SES or environmental factors associated with a higher parity (194). Residual confounding may therefore be contributing to the association observed between HIV/ART exposure and infectious disease admissions in these analyses.

Low / very low / extremely low birth weight were associated with increased risk of hospitalisation in both children HEU and HUU across the neonatal, postneonatal and >12 months – 36 months age groups. Although studies have reported an association between maternal HIV and ART exposure and an increased risk of adverse birth outcomes, the results for low birth weight as an adverse outcome have been inconsistent (115,195,196). Low birth weight infants have an increased risk of morbidity, including hospitalisation (197,198). In this cohort, it is evident that low birth weight infants are a high risk group that require closer monitoring beyond age 1 year for both children HEU and HUU. The excess risk of hospitalisation among low/very low/extremely low, compared to normal birth weight children was higher for children HUU than HEU, indicating that low birth weight may be more of a driving factor for infectious disease hospitalisation among children HUU in the absence of the effects of HIV and ART exposure. Despite some attenuation of the positive association between multiple pregnancy (e.g. twins) status and infection-related admissions after controlling for other factors such as low birth weight, multiple pregnancy was associated with a higher risk of admission during the postneonatal period. This is likely due to suboptimal *in utero* environmental (e.g. micronutrient deficiencies) and postnatal (e.g. suboptimal breastfeeding) conditions that I was unable to account for (199,200). I found an association between maternal viral load during pregnancy and infection-related hospitalisations, among children HEU, during the postneonatal period. This is similar to findings from other studies (17,23).

Strengths and limitations:

This analysis provides the largest population level assessment of infectious disease outcomes in children HEU relative to HUU to date. With enrolment of children born up till the end of 2018 and the implementation of Universal ART for all people living with HIV in 2016, I was able to analyse the effect of HIV exposure through a period of a) greater access to maternal and pre-pregnancy ART and b) encouraged exclusive breastfeeding for 6 months with extended mixed feeding thereafter up to age 24 months. Furthermore, as this study had a large sample size, I was able to stratify HIV exposure status by timing of maternal ART start,

enabling me to compare the associations of HIV and ART exposure in children HEU to those HUU, as opposed to only comparing timing of ART start among children HEU.

Reliable breastfeeding and gestational age data, both of which have been reported to be important factors associated with infectious disease outcomes among children HEU (17,23,24), are not available within the WCPHDC. I was therefore not able to assess their impact on the results observed. Other potential determinants of infectious diseases which I was not able to assess include: water, sanitation and hygiene practices, immunisation, overcrowding, number of immunocompromised individuals per household and malnutrition. Furthermore, as discussed in Chapter 1, one frequent limitation of research in this field is lack of adjustment for confounding variables. Prior to analysis, I constructed a DAG to consider the relationship among factors potentially associated with HIV/ART exposure and/or infectious disease hospitalisations. I was able to adjust for maternal age and suburb of residence as a proxy of SES. However, unfortunately I was not able to adjust for other potential confounders such as maternal education and substance use. Therefore, estimates from this study should not be interpreted as causal.

A further limitation is that I did not account for children relocating into and out of the WC and out of hospital deaths, all of which may be differential by HIV exposure and ART status, and may therefore have underestimated hospitalisations and deaths. If out of province relocations and out of hospital death were more common in children HEU vs. HUU, it's likely that the estimated associations between HIV/ART exposure and hospitalisation are underestimated.

The classification of ART exposure is also subject to ascertainment bias. Mothers for whom there is no electronic record of ART dispensing, and their children, may be accessing healthcare in the private sector, may have relocated to another province, or may be deceased. The association of HIV/ART exposure in this group, relative to children HUU, should therefore be interpreted with caution. Relocation between provinces and accessing private sector healthcare may have also resulted in misclassification of the other ART exposure variables. Furthermore, due to lack of gestational age data and the use of 42 weeks before delivery as the estimated start of delivery, mothers may be misclassified as starting ART during pregnancy, rather than before pregnancy, if they delivered preterm.

Additionally, given that the proportion of mother and child in-hospital deaths is higher among children excluded vs. included in these analyses, it's possible that my sample is subject to selection bias if excluded children, of which a greater proportion were HIV-exposed, were more sickly and more likely to be hospitalised. This would mean that the observed estimates of the association between maternal HIV/ART and child infectious disease admissions in this chapter may be underestimated. However, almost 30% of the excluded children were born with HIV or had an unknown HIV status prior to their first HIV evidence and likely accounted for a substantial proportion of the recorded deaths.

As only four types of infections were considered for hospital admissions, many other neonatal infections were likely excluded (e.g. sepsis, necrotising enterocolitis, and congenital infections). It's therefore possible that the relative risk of admission, among children HEU vs. HUU, during the neonatal period is underestimated.

Conclusions:

In conclusion, this large population-level cohort illustrates that, even with greater access to maternal and pre-pregnancy ART, children HEU vs. HUU are at increased risk of infection-related hospitalisation, particularly during the neonatal period. Given the size of the population of children HEU, this is an additional burden on an already strained healthcare system. The excess risk of hospitalisation was attenuated in the postneonatal period, compared to the neonatal period, among children HEU whose mothers started ART during pregnancy, and, after age 12 months, children HEU whose mothers either started ART before pregnancy and during Universal ART or during pregnancy had a reduced risk of hospitalisation compared to children HUU. Moreover, children HEU whose mothers restarted ART during pregnancy or were not on ART during pregnancy had the highest risk of hospitalisation relative to children HUU. Interventions to support maternal ART initiation and adherence could help to partially mitigate the excess risk of infection-related hospitalisation among children HEU, but this alone will not be enough to ensure that these children have health outcomes comparable to their HUU counterparts. As suggested by others, scaling up of interventions to promote optimal breastfeeding and vaccination are urgently needed to reduce infectious disease morbidity in both children HEU and HUU (17,24). In addition, it's important to consider the household, environmental, community and societal factors

associated with being a child affected by HIV (130), as well as engagement in care of both mothers and children.

CHAPTER 6. HEALTHCARE UTILISATION FOR WELL-CHILD VISITS COMPARED BY MATERNAL HIV STATUS AND ENGAGEMENT IN HIV VERTICAL TRANSMISSION PREVENTION SERVICES

6.1. Chapter overview

Chapter 5 compared the rates of infectious disease hospital admissions by HIV and ART exposure status among children born in the WC between 2013 and 2018. The results showed that, despite being born in an era in which guidelines support improved access to maternal ART and recommend exclusive breastfeeding, children HEU vs. HUU remain at increased risk of infection-related hospitalisation in the first year of life. Moreover, the increased risk of hospitalisation was particularly high among children HEU whose mothers were not on ART during pregnancy or restarted ART during pregnancy after a gap in care. In contrast, during the >12 – 36-month age period, children HEU whose mothers either started ART before pregnancy and during the Universal ART period or during pregnancy had a reduced risk of hospitalisation compared to their HUU counterparts.

Studies have previously reported that antenatal maternal engagement in care is associated with better engagement in postnatal paediatric care (e.g. immunisation) (168,190). The observations from the analyses in Chapter 5 lead to the question of whether maternal ART adherence as a proxy for maternal engagement in antenatal care is associated with better routine child healthcare clinic visit utilisation and whether this could play a role in mitigating some of the increased risk of infectious-cause morbidity amongst children HEU in the first year of life.

This chapter therefore investigated whether routine child healthcare clinic visits, up to 18 months of age, differed by maternal engagement in HIV VTP services (using maternal ART engagement as a proxy), in this cohort of children.

6.2. Introduction

Routine child healthcare clinic visits for developmental milestone and growth monitoring and immunisations (known in SA as "well-child" visits) are important for preventative and promotive healthcare in children (201). Child morbidity and mortality rates from vaccine-preventable, malnutrition and HIV-related illnesses remain high in SA and attendance at well-child visits provides opportunities for early intervention (201). Missed well-child visits could negatively impact a child's future.

In SA and the WC it is recommended that all infants/children attend routine well-child visits (these visits include, growth monitoring, developmental screening and/or the administration of the Expanded Programme on Immunisation vaccines) at six, ten and 14 weeks of age, monthly up to one year of age, and every third month thereafter, until 18 months of age (202). Concurrent to the well-child visits, guidelines in use during the study period also recommended that children who are HIV-exposed, and not on child antiretroviral therapy (ART), receive routine HIV testing at birth, six/ten weeks, nine months and 18 months of age (31,35).

Despite effective well-child and prevention of vertical HIV transmission programmes that could save lives, coverage gaps exist. Substantial loss-to-follow-up of children who are HEU at postnatal points in the prevention of vertical HIV transmission cascade has been reported (203). A SA study observed that, among children HEU, 31% missed their age 18-month well-child visit (204). Mothers who hadn't initiated ART by 6 weeks postpartum, who were ≤24 years of age or who had to travel further to the clinic were more likely to miss visits. Furthermore, the 2017/18 District Health Barometer reported that only 22% of infants who were HIV-exposed in the WC were estimated to receive the recommended HIV test at 18 months of age (108).

The proportion of SA mothers living with HIV and disengaging from ART care is high, particularly during the postnatal period, with up to 26% of these mothers having been reported to have disengaged from care by one year postpartum (205–208). Furthermore, a recent study by Phillips *et al.* indicated that maternal postpartum engagement differs by prior ART history (208). Very little is known about the relationship between maternal healthcare

engagement among mothers with HIV and well-child healthcare engagement. Mothers with HIV may ensure their children attend regular well-child visits because they are more concerned for their health or because of additional HIV-related services at these visits (e.g. child HIV testing and postnatal prophylaxis). Additionally, mothers who have engaged in HIV care and started ART, and thus had more regular contact with services, may have more engagement with child health services due to being more familiar with these services and/or having better access to healthcare. Alternatively, mothers with HIV may engage less with child health services as they may be a vulnerable group with poorer socio-economic status, less access to healthcare and may experience stigma. Furthermore, an estimated 75% of the WC population, and likely higher for people living with HIV and children (although not formally documented), utilise public healthcare facilities (148). It's therefore likely that the majority of children HEU will attend well-child visits at public health facilities and would face similar barriers to accessing care as their mothers.

This analysis aimed to determine whether healthcare utilisation up to 18 months of age for well-child visits in this study cohort of children born between 2013 and 2018 differs by maternal HIV status and engagement in HIV VTP services. I, a) described the completion of well-child visits at each selected timepoint, by HIV exposure status and maternal engagement in VTP services, b) described the number of missed well-child visits (from 0 – 7) by HIV exposure status and maternal engagement in VTP services, and c) assessed whether the number of missed well-child visits among children HEU differs by maternal engagement in VTP services, and d) identified factors associated with missed well-child visits among children HEU.

6.3. Methods

6.3.1. Study design, data source and study setting

Details of the study design, data source, and study setting have been described in Chapter 2 – sections 2.2 and 2.3.

6.3.2. Study participants

The inclusion and exclusion criteria for the analyses in this chapter are described in Chapter 2– section 2.4. I included the same cohort of children who were included for Chapter 5, with additional exclusions. As explained in Chapter 2– section 2.4, there is ongoing improvement of the unique identifiers within the WCPHDC and because additional data extraction for Chapter 6 was completed a year after the data extraction for Chapters 3 – 5, there were mother-child and sibling linkages from the initial extraction that were no longer considered robust by the WCPHDC in the most recent extraction. These mother-child pairs were therefore excluded from analyses in this chapter. Additionally, as children from multiple pregnancies are likely to attend the same well-child visits, I randomly selected one child from each multiple pregnancy for inclusion and excluded the additional twins/triplets/quadruplets from analyses. The number of children included and excluded from analyses is described in Figure 6.1. I compared the key non-HIV related characteristics of those included in vs. excluded from these analyses to assess potential selection bias in my sample (Appendix Table 6.1).

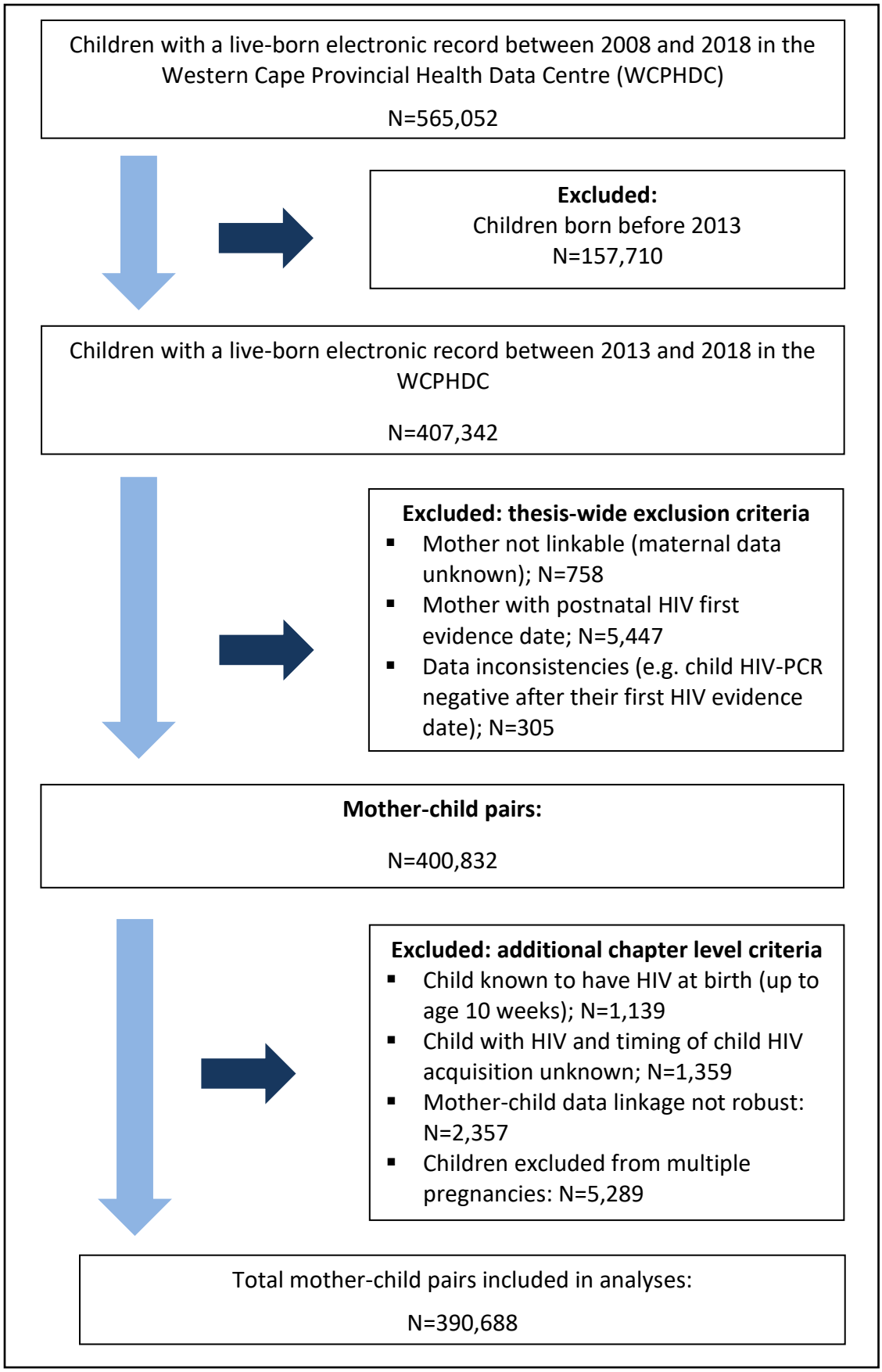


Figure 6.1: Flow diagram of mother-child pairs included in the cohort of children, born in the Western Cape (2013 – 2018) and used for the analyses in Chapter 6

6.3.3. Procedures and measurements

The overarching data cleaning, management and extraction that I carried out for this chapter is described in Chapter 2– section 2.5. For this chapter, I used the same data that was used for Chapter 5 including child and mother date of birth, child sex, child birth weight, multiple pregnancy status, parity, and suburb of residence, for mother and child descriptive statistics and assessing factors associated with missed well-child visits. If the mother or child died in-facility during the study period (up to age two years), date of death was used for descriptive statistics, to determine follow-up time (for children) and to assess the association of maternal death with missed well-child visits. Using the most up-to-date unique mother and child identifiers at the time of these analyses, I extracted de-duplicated child primary healthcare visit encounter data (date of encounter, encounter facility) within the WCPHDC, between infant date of birth and age 2 years and used these as a proxy for well-child visits (as the reason for each primary health visit (well-child vs. other) is not recorded in the WCPHDC). I also extracted up-to-date mother ART start date, maternal ART dispensing dates between 6 months before estimated pregnancy start and child date of birth, and mother "last ART in hand date" (last ART dispensing date + prescription length). For children HEU, I used mother and child HIV first evidence dates, maternal ART start date, maternal ART dispensing dates, and "last ART in hand dates" to define child HIV exposure and maternal engagement in HIV VTP services. I used mother and child laboratory test results (HIV PCR and ELISA) for the classification of child HIV exposure status certainty and to calculate follow-up time if a child had evidence of having HIV.

Exposure

The exposures of interest were HIV exposure status and maternal engagement in HIV VTP services. Children were classified as *in utero* HEU and HUU (regardless of certainty) at the start of follow-up. Certainty of HIV exposure and infection status at the end of follow-up was categorised using the definitions described in Chapter 3. I defined a categorical variable, maternal ART engagement during pregnancy, as a proxy for maternal VTP engagement. This was based on both maternal ART start date and any evidence of gaps in ART during pregnancy. I defined gaps in engagement in VTP services during pregnancy as a period of >28 days, between previous "last ART in hand date" and the next ART dispensing date, and at least 29

days of that period was between pregnancy estimated start date and child date of birth. I defined timing of maternal ART start as before pregnancy (≥42 weeks before child date of birth), during pregnancy (<42 weeks before child date of birth and before child date of birth), or at delivery/postpartum.

I categorised maternal ART engagement during pregnancy as follows (Table 6.1)[e]:

[e]Maternal ART engagement during pregnancy in this chapter differs from the HIV/ART exposure variable used in Chapter 5 in that it takes gaps in maternal ART throughout pregnancy into account. The HIV/ART exposure variable used in Chapter 5 classified maternal ART restart during pregnancy, which was a gap of no ART during the first trimester of pregnancy, but did not consider any further ART gaps during pregnancy.

Table 6.1: Definition criteria for the classification of maternal ART engagement during pregnancy

ART engagement group		Definition criteria (all conditions in each category must hold true)
ART start before pregnancy	No gap in engagement	▪ Maternal ART started ≥42 weeks before child date of birth ▪ No evidence of a gap[¥] in maternal ART during pregnancy
	Gap in engagement	▪ Maternal ART started ≥42 weeks before child date of birth ▪ Evidence of a gap in maternal ART during pregnancy
ART start during pregnancy	No gap in engagement	▪ Maternal ART start >0 and <42 weeks before child date of birth ▪ No evidence of a gap in maternal ART during pregnancy, after ART start
	Gap in engagement	▪ Maternal ART start >0 and <42 weeks before child date of birth ▪ Mother with HIV first evidence date during pregnancy and started ART >14 days after HIV first evidence OR mother with HIV first evidence date before pregnancy and started ART > 28 days after estimated pregnancy start[†] OR had evidence of a gap in maternal ART that occurred after ART start during pregnancy
ART start at delivery/postpartum		▪ Maternal ART start on or after child date of birth
Unknown ART gaps		▪ Maternal ART start date before or during pregnancy but had no electronic evidence of ART dispensing during pregnancy
No ART evidence ever		▪ Maternal HIV first evidence date, but no ART start date

[¥]Gaps in maternal ART during pregnancy were defined as a period of >28 days, between previous "last ART in hand date" (dispensing date + length of prescription) and the next ART dispensing date, with at least 29 days of that period falling between pregnancy estimated start date and child date of birth

[†]Pregnancy start was approximated as 42 weeks before infant date of birth

Abbreviations – ART: antiretroviral therapy

Outcomes

Follow-up time was from date of birth until the earliest of: date of last negative HIV test result for children with a subsequent positive HIV diagnostic test, in-hospital death, or age two years. It is recommended that children have seven well-child visits by 18 months of age. The primary outcome of this chapter was number of missed well-child visits. The number of missed visits for each child was determined by the difference between their total actual visits and the number of visits for which the child was eligible during the follow-up period. For example, if a child's end of follow-up was at age seven months, they would be eligible for four out of seven well-child visits.

I chose well-child visit timepoints based on the ages recommended for immunisation visits and HIV testing, as described in the introduction of this chapter. I considered child primary healthcare encounters to be well-child visits if they were at a clinic, community health centre, community day centre, midwife obstetrics unit or mobile service and occurred within the windows of infant age described in (Table 6.2). I excluded child encounters that were hospitalisations.

Table 6.2: Well-child visit timepoints and corresponding windows during which a primary healthcare encounter was considered a well-child visit

Well-child visit timepoint	**Encounter window - age (days after child birth)**
6 weeks	≥21 and ≤56
10 weeks	≥57 and ≤84
14 weeks	≥85 and ≤133
6 months	≥134 and ≤210
9 months	≥211 and ≤294
12 months	≥295 and ≤420
18 months	≥421 and ≤731

Confounders

I considered maternal age at child birth and suburb of residence (as a proxy for socioeconomic status) to be potential confounders of the association between maternal ART engagement and missed well-child visits, decided a priori using a directed acyclic graph (Figure 6.2)[f]. These are defined in Chapter 2 – section 2.6. There are likely others factors confounding the association between maternal ART engagement and missed well-child visits, e.g. maternal education, maternal substance abuse, maternal mental health, but data on these was not available.

Factors associated with missed well-child visits

I considered the following potential factors associated with missed well-child visits: birth weight, multiple pregnancy status, parity, and maternal death before child age two. These are defined in Chapter 2 – section 2.6.

[f] The directed acyclic graph includes additional factors that could not be included in the analyses.

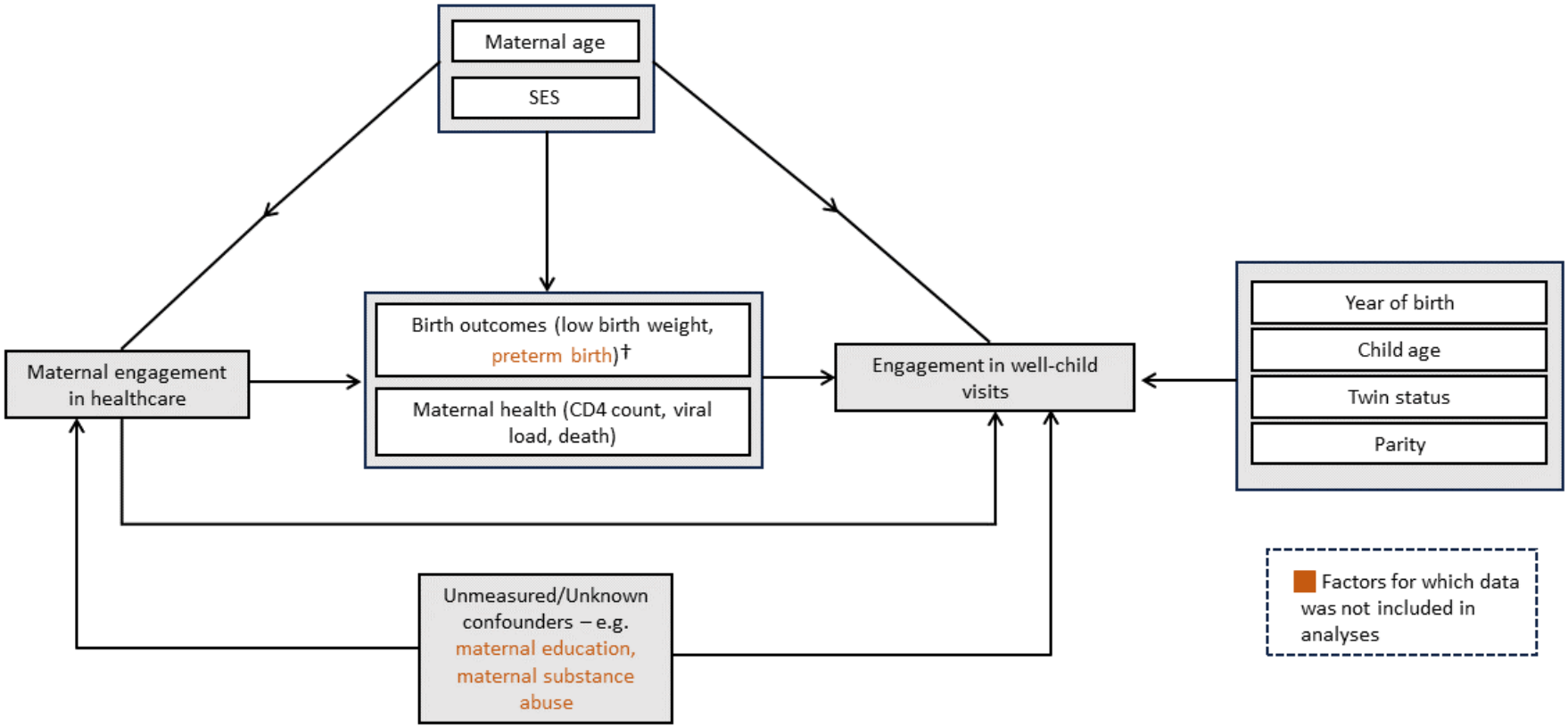


Figure 6.2: Directed acyclic graph representing the hypothesised relationships between maternal engagement in healthcare, other factors, and engagement in well-child visits

†Birth outcomes can only mediate the association between maternal engagement in healthcare and child engagement in well-child visits if mothers started ART before child date of birth.

Abbreviations – SES: Socioeconomic status

6.3.4. Statistical analyses

I described key maternal and child characteristics, by HIV exposure status, using proportions for categorical variables; for continuous variables I used means with standard deviations, or - for variables with obvious skew (based on histograms) - medians with first and third quartiles. I used proportions to describe the completion of visit attendance, among children eligible for a visit, at each of the seven well-child visits, for children HUU and by maternal ART engagement status for children HEU. I first described the completion of attendance at visits among all children born between 2013 and 2018 and then restricted the analysis to children born in 2017 and 2018 as these years had better electronic capture of routine healthcare data. For children born between 2013 and 2018, I described the proportion of children in each category of number of missed well-child visits (each category is an integer between 0 and 7), for children HUU and by maternal ART engagement status for children HEU. These proportions were calculated as number of children who missed n number of visits out of the number of children eligible for ≥n visits.

I used mixed effects Poisson regression to assess the association between maternal ART engagement and the number of missed well-child visits, as well as potential factors associated with missed visits. Only children HEU and those eligible for ≥1 visit were included in the models. The models included number of eligible visits as an offset to account for the varying time for which children were eligible for a visit. All models were controlled for child-level (i.e. child identifier) random effects to account for correlated well-child visits within an individual child. Where suburb was included as a covariate (adjusted models), this was also modelled as a random effect to control for clustering within suburbs. I assessed the unadjusted association between independent variables and missed well-child visit count. I then assessed the adjusted association between maternal ART engagement and number of missed well-child visits, controlling for maternal age and suburb as potential confounders (Model A). I extended the above model to incorporate other potential factors associated with missed well-child visits (Model B). As was done with the completion of attendance analysis, I did a sensitivity analysis by restricting the above regression models to children born in 2017 and 2018. Analyses were done using Stata 17.0 (177).

6.4. Results

6.4.1. Characteristics of children and mothers

As in Chapter 5, 407,342 children had a live-born electronic record in the WCPHDC between 2013 and 2018. Of these children, 390,688 (95.9%) mother-child pairs were included in the analyses for this chapter (Figure 6.1). The characteristics of included children and mother are shown in Table 6.3. Appendix Table 6.1 compares the characteristics of included and excluded children. Among children included, 17.1% were HEU, 50.6% were male, 16.8% of children HEU vs. 15.2% of children HUU had birth weight <2500g, and 1.8% of children HEU vs. 1.3% of children HUU were multiple pregnancies. 98.8% of the cohort (98.3% of children HEU and 99.0% of children HUU) were eligible for all 7 visits during follow-up. The mean maternal age at child birth was 29.8 years for children HEU and 26.9 years for children HUU. Among mothers of children HEU, 19.9% started ART before pregnancy and had no gaps in ART dispensed during pregnancy. In-hospital maternal death by age 2 years was 0.6% for children HEU and 0.1% for children HUU.

Table 6.3: Characteristics of children (and their mothers), born in Western Cape from 2013 – 2018, by HIV exposure and infection status at the start of follow up

Variable	Total N=390,688 (100.0%)	Children HEU N=66,875 (17.1%)	Children HUU N=323,813 (82.9%)
	Child characteristics		
Sex:			
Male	197,770 (50.6)	33,847 (50.6)	163,923 (50.6)
Missing	777 (0.2)	155 (0.2)	622 (0.2)
Birth weight (g):			
Foetal macrosomia (≥4000)	16,486 (4.2)	2,301 (3.4)	14,185 (4.4)
Normal (2500 – <4000)	312,536 (80.0)	53,153 (79.5)	259,383 (80.1)
Low (1500 – <2500)	50,366 (12.9)	9,257 (13.8)	41,109 (12.7)
Very low (1000 – <1500)	6,698 (1.7)	1,395 (2.1)	5,303 (1.6)
Extremely low (<1000)	3,347 (0.9)	567 (0.9)	2,780 (0.9)
Missing	1,255 (0.3)	202 (0.3)	1,053 (0.3)
Multiple pregnancy:			
Yes	5,467 (1.4)	1,230 (1.8)	4,237 (1.3)
Missing	140 (0.04)	36 (0.05)	104 (0.03)
Birth year			
2013 & 2014	99,326 (25.4)	15,038 (22.5)	84,288 (26.0)
2015 & 2016	133,081 (34.1)	22,603 (33.8)	110,478 (34.1)
2017 & 2018	158,281 (40.5)	29,234 (43.7)	129,047 (39.9)

Variable	Total N=390,688 (100.0%)	Children HEU N=66,875 (17.1%)	Children HUU N=323,813 (82.9%)
Subdistrict of residence:			
Metropolitan	263,723 (67.5)	49,947 (74.7)	213,776 (66.0)
Non-metropolitan	120,882 (30.9)	16,077 (24.0)	104,805 (32.4)
Missing	6,083 (1.6)	851 (1.3)	5,232 (1.6)
HIV first evidence following a negative HIV test result: n(%)			
Yes	387 (0.1%)	362 (0.5)	25 (0.01)
Died before 2 years of age (all-cause): n (%)			
Yes	4,238 (1.1)	788 (1.2)	3,450 (1.1)
Number of well-child visits eligible for:			
0	3170	562 (0.8)	2,608 (0.8)
1	294	79 (0.1)	215 (0.1)
2	284	179 (0.3)	105 (0.03)
3	313	131 (0.2)	182 (0.06)
4	183	74 (0.1)	109 (0.03)
5	129	54 (0.1)	75 (0.02)
6	160	46 (0.1)	114 (0.04)
7	386,155 (98.8)	65,750 (98.3)	320,405 (99.0)
Maternal Characteristics			
Age at delivery (years):			
15 – 19	47,483 (12.2)	2,335 (3.5)	45,148 (13.9)
20 – 39	330,540 (84.6)	61,926 (92.6)	268,614 (83.0)
40 – 50	11,293 (2.9)	2,556 (3.8)	8,737 (2.7)
Mean (sd)	27.4 (6.2)	29.8 (5.7)	26.9 (6.2)
Missing:	1,372 (0.4)	58 (0.1)	1,314 (0.4)
Parity[¥]:			
0	242,736 (62.1)	37,728 (56.4)	205,008 (63.3)
1	103,789 (26.6)	20,190 (30.2)	83,599 (25.8)
2	33,032 (8.5)	6,876 (10.3)	26,156 (8.1)
≥3	11,071 (2.8)	2,069 (3.1)	9,002 (2.8)
Missing	60 (0.02)	12 (0.02)	48 (0.01)
Maternal death by child age 2 years:			
Yes	825 (0.2)	424 (0.6)	401 (0.1)
Maternal ART engagement			
ART start before pregnancy – no gaps	–	13,311 (19.9)	–
ART start before pregnancy – gaps	–	11,529 (17.2)	–
ART start during pregnancy – no gaps	–	12,360 (18.5)	–
ART start during pregnancy – gaps	–	12,770 (19.1)	–
ART start at delivery/ postpartum	–	5,033 (7.5)	–
ART unknown	–	9,749 (14.6)	–
No ART evidence ever	–	2,124 (3.2)	–

[¥]Parity is recorded during current pregnancy and is based on digital evidence of prior pregnancies in the Western Cape only. This may therefore underestimate actual parity, especially for earlier pregnancies when the use of digital systems was less complete.

Abbreviations – ART: antiretroviral therapy; g: grams; HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected

6.4.2. Well-child visits

Table 6.4 shows the electronically recorded completion of attendance at well-child visits, by HIV exposure status and initiation of and adherence to maternal ART, among children born in 2013 to 2018. Among children HUU, well-child visit coverage was 36.1% and 42.6% at 6 weeks and 12 months, respectively. Among children HEU whose mothers started ART before pregnancy, and had no gaps in ART dispensed during pregnancy, well-child visit coverage was the highest with 61.8% and 55.9% of eligible children having had well-child visits at ages six weeks and 12 months respectively. Among children HEU whose mothers started ART before pregnancy, and had a gap in ART dispensed during pregnancy, coverage was lower with 57.3% and 48.1% of those eligible attending well-child visits at ages six weeks and 12 months respectively. In children HEU whose mothers started ART at delivery or postpartum, the proportion of those eligible who attended well-child visits at ages six weeks and 12 months was even lower at 48.9% and 29.4% respectively.

Table 6.5 shows the completion of attendance at well-child visits, by HIV exposure status and initiation of and adherence to maternal ART, among children born in 2017 and 2018. In both children HUU and children HEU (all ART groups), coverage of well-child visits among children born in 2017 and 2018 was higher compared to when including children born from 2013 to 2018 (Table 6.4) but with a similar pattern of lower coverage among children whose mothers had ART gaps during pregnancy or only started ART at delivery or postpartum. Among children HEU who were born in 2017 and 2018, recorded completion of attendance at well-child visits was highest at age 10 weeks for all maternal ART adherence categories, except for those that had no maternal ART evidence ever.

Table 6.6 describes the proportion of children who missed different numbers (0 – 7) of well-child visits among children born between 2013 and 2018. Among children HUU, 85.6% missed ≥1 visit and 31.1% missed all seven visits. Among children HEU, 83.0% missed ≥1 visit and 19.9% missed all seven visits. Children HEU whose mothers started ART before pregnancy, with no gaps in dispensed ART, had the highest proportion of zero missed visits (25.5%) and lowest proportion of all seven missed visits (15.2%). In children HEU whose mothers started ART at delivery or postpartum, 8.1% had zero missed visits, while 29.8% missed all seven visits.

Table 6.4: Completion of attendance at well-child visits, by initiation of and adherence to maternal ART (as a proxy of maternal engagement of vertical HIV transmission prevention services), for children born in 2013 to 2018

		Children HEU							
Visit **Eligible N (% visit complete)**	**Children HUU**	**ART start before pregnancy – no gaps**	**ART start before pregnancy – gaps**	**ART start during pregnancy – no gaps**	**ART start during pregnancy – gaps**	**ART start at delivery/ postpartum**	**Unknown ART¥**	**No ART evidence ever**	**Total children HEU**
6 weeks	321,205 (36.1)	13,217 (61.8)	11,429 (57.3)	12,263 (57.1)	12,690 (56.1)	4,948 (48.9)	9,666 (55.2)	2,100 (44.7)	66,313 (56.6)
10 weeks	320,990 (32.2)	13,209 (60.4)	11,409 (55.0)	12,250 (48.7)	12,680 (45.1)	4,932 (31.4)	9,657 (49.1)	2,097 (36.4)	66,234 (49.8)
14 weeks	320,885 (36.7)	13,189 (55.3)	11,351 (51.0)	12,234 (44.5)	12,644 (42.2)	4,922 (29.4)	9,624 (46.0)	2,091 (36.8)	66,055 (46.2)
6 months	320,703 (39.0)	13,176 (55.9)	11,318 (50.8)	12,216 (43.7)	12,619 (41.5)	4,911 (29.6)	9,596 (45.4)	2,088 (38.8)	65,924 (46.0)
9 months	320,594 (39.6)	13,167 (55.2)	11,299 (48.0)	12,209 (42.6)	12,602 (40.3)	4,901 (29.4)	9,584 (44.4)	2,088 (37.0)	65,850 (44.7)
12 months	320,519 (42.6)	13,160 (55.9)	11,288 (48.1)	12,195 (42.1)	12,592 (40.5)	4,896 (29.4)	9,578 (44.5)	2,087 (38.4)	65,796 (44.9)
18 months	320,405 (50.8)	13,154 (61.1)	11,280 (53.1)	12,187 (46.9)	12,581 (45.7)	4,893 (35.8)	9,569 (51.4)	2,086 (44.4)	65,750 (50.3)

¥ Mothers who had evidence of starting ART before or during pregnancy, but no electronic evidence of ART dispensing during pregnancy

Abbreviations – ART: Antiretroviral therapy; HUU: HIV unexposed and uninfected; HEU: HIV exposed and uninfected

Table 6.5: Completion of attendance at well-child visits, by initiation of and adherence to maternal ART (as a proxy of maternal engagement of vertical HIV transmission prevention services), for children born in 2017 to 2018

		Children HEU							
Visit **Eligible N (% visit complete)**	**Children HUU**	**ART start before pregnancy – no gaps**	**ART start before pregnancy – gaps**	**ART start during pregnancy – no gaps**	**ART start during pregnancy – gaps**	**ART start at delivery/ postpartum**	**Unknown ART¥**	**No ART evidence ever**	**Total children HEU**
6 weeks	128,021 (56.7)	7,170 (67.7)	6,227 (62.1)	4,663 (61.3)	4,486 (60.4)	1,236 (54.9)	4,230 (59.8)	935 (50.9)	28,947 (62.1)
10 weeks	127,944 (52.2)	7,163 (76.6)	6,217 (68.9)	4,657 (69.0)	4,483 (66.9)	1,234 (61.7)	4,225 (67.6)	933 (53.5)	28,912 (69.5)
14 weeks	127,913 (58.9)	7,149 (73.0)	6,174 (66.8)	4,647 (65.0)	4,461 (63.8)	1,228 (57.7)	4,203 (66.1)	930 (56.3)	28,792 (66.8)
6 months	127,848 (62.6)	7,141 (74.5)	6,154 (67.5)	4,640 (65.7)	4,447 (64.0)	1,224 (58.3)	4,192 (66.4)	928 (61.5)	28,726 (67.7)
9 months	127,799 (63.1)	7,136 (73.6)	6,142 (63.5)	4,638 (64.0)	4,441 (62.4)	1,223 (56.0)	4,185 (63.9)	928 (59.4)	28,693 (65.5)
12 months	127,766 (63.8)	7,130 (73.0)	6,138 (61.9)	4,636 (61.5)	4,439 (60.7)	1,222 (55.6)	4,182 (62.8)	928 (59.1)	28,675 (64.2)
18 months	127,723 (65.2)	7,129 (71.9)	6,134 (62.5)	4,633 (60.7)	4,438 (60.0)	1,221 (52.9)	4,178 (62.6)	928 (59.8)	28,661 (63.7)

¥ Mothers who had evidence of starting ART before or during pregnancy, but no electronic evidence of ART dispensing during pregnancy

Abbreviations – ART: Antiretroviral therapy; HUU: HIV unexposed and uninfected; HEU: HIV exposed and uninfected

Table 6.6: Number of missed well child visits[¥], by initiation and adherence of maternal ART (as a proxy of maternal engagement in vertical HIV transmission prevention services), for children born in 2013 to 2018

		Children HEU							
Missed visits Eligible N (% with relevant number of missed visits)	**Children HUU**	**ART start before pregnancy– no gaps**	**ART start before pregnancy – gaps**	**ART start during pregnancy – no gaps**	**ART start during pregnancy – gaps**	**ART start at delivery/ postpartum**	**Unknown ART[†]**	**No ART evidence ever**	**Total children HEU**
0	321,205 (14.4)	13,217 (25.5)	11,429 (18.0)	12,263 (15.5)	12,690 (13.6)	4,948 (8.1)	9,666 (16.1)	2,100 (13.1)	66,313 (17.0)
1	321,205 (9.3)	13,217 (14.4)	11,429 (14.0)	12,263 (10.1)	12,690 (10.5)	4,948 (7.0)	9,666 (11.6)	2,100 (9.0)	66,313 (11.7)
2	320,990 (6.9)	13,209 (9.9)	11,409 (10.8)	12,250 (9.5)	12,680 (9.12)	4,932 (6.1)	9,657 (9.4)	2,097 (7.6)	66,234 (9.4)
3	320,885 (7.3)	13,189 (9.6)	11,351 (10.4)	12,234 (10.3)	12,644 (9.6)	4,922 (8.0)	9,624 (10.5)	2,091 (8.6)	66,055 (9.8)
4	320,703 (8.2)	13,176 (9.5)	11,318 (10.5)	12,216 (11.3)	12,619 (11.2)	4,911 (10.6)	9,596 (11.2)	2,088 (8.7)	65,924 (10.6)
5	320,594 (9.5)	13,167 (9.5)	11,299 (10.6)	12,209 (12.3)	12,602 (13.2)	4,901 (14.3)	9,584 (11.9)	2,088 (11.4)	65,850 (11.7)
6	320,519 (13.4)	13,160 (6.6)	11,288 (8.9)	12,195 (11.7)	12,592 (12.0)	4,896 (16.9)	9,578 (9.9)	2,087 (12.4)	65,796 (10.4)
7	320,405 (31.1)	13,154 (15.2)	11,280 (17.5)	12,187 (19.7)	12,581 (21.4)	4,893 (29.8)	9,569 (19.9)	2,086 (29.8)	65,750 (19.9)

[¥]The number of missed well child visits was calculated as the number of visits a child was eligible for (depending on their follow-up time) minus number of visits attended. The proportion of children who missed n number of visits was calculated as a proportion of the children eligible for ≥n visits.

[†]Mothers who had evidence of starting ART before or during pregnancy, but no electronic evidence of ART dispensing during pregnancy

Abbreviations – ART: Antiretroviral therapy; HUU: Unexposed to HIV and uninfected; HEU: Exposed to HIV and uninfected

Table 6.7 shows findings from unadjusted and adjusted Poisson analyses among children born from 2013 to 2018. Unadjusted Poisson regression analysis showed that maternal ART engagement was associated with missed well-child visits, with more missed visits in each other group relative to children whose mothers started ART before pregnancy and had no gaps. Children whose mothers started ART before pregnancy and had gaps in dispensed ART had a 16% increased rate in missed visits compared to those whose mothers started ART before pregnancy and had no gaps in dispensed ART (uIRR=1.16; 95% CI:1.14-1.18). Children whose mothers started ART at delivery/postpartum were the most likely to miss visits relative to those whose mothers started ART before pregnancy and had no gaps in dispensed ART (uIRR=1.66; 95% CI:1.62-1.70). When adjusting for maternal age and suburb of residence (Model A), associations between maternal ART engagement and number of missed well-child visits remained similar to the unadjusted model. In the multivariable model including additional potential factors associated with missed well-child visits (Model B), maternal ART engagement remained associated with higher rates of missed visits, although at an attenuated level compared to in Model A. Maternal age 40–50 years, vs. 15-19 years, was associated with a reduced rate of missed visits (aIRR=0.94; 95% CI:0.90-0.97). Parity ≥3, compared to 0, was associated with higher rates of missed well-child visits (aIRR=1.08; 95% CI:1.05-1.12). Maternal death before child age 2 years, vs. mother being alive at child age 2 years, was also associated with an increased risk of missed-visits (aIRR=1.07; 95% CI:1.01-1.14).

When restricting to children born in 2017 and 2018, maternal ART engagement remained associated with missed well-child visits for all categories compared to mothers starting ART before pregnancy with no gaps (Table 6.8). Furthermore, the magnitude of these estimated associations was increased slightly (compared to estimates when including children born from 2013 to 2018), ranging from (aIRR=1.35; 95% CI:1.30-1.40) for children whose mothers started ART before pregnancy, with gaps, to (aIRR=1.67; 95% CI:1.57-1.78) for children whose mothers had no evidence of ART dispensing ever, when controlling for maternal age and suburb of residence as potential confounders.

Table 6.7: Poisson regression models assessing associations with number of missed well child visits[¥] in HEU infants, born between 2013 and 2018, up to age 2 years

	Unadjusted models	Model A	Model B
	uIRR (95%CI)	**aIRR (95%CI) (N=65,420)**	**aIRR (95%CI) (N=65,204)**
Maternal ART engagement			
ART start before pregnancy – no gaps	Reference	Reference	Reference
ART start before pregnancy – gaps	1.16 (1.14-1.18)	1.16 (1.14-1.18)	1.15 (1.13-1.17)
ART start during pregnancy – no gaps	1.30 (1.28-1.33)	1.30 (1.27-1.32)	1.16 (1.14-1.18)
ART start during pregnancy – gaps	1.36 (1.33-1.38)	1.35 (1.32-1.37)	1.17 (1.15-1.19)
ART start at delivery/postpartum	1.66 (1.62-1.70)	1.63 (1.59-1.67)	1.26 (1.23-1.29)
Unknown ART[†]	1.26 (1.24-1.29)	1.26 (1.23-1.28)	1.16 (1.14-1.18)
No ART evidence ever	1.48 (1.43-1.53)	1.47 (1.42-1.52)	1.32 (1.28-1.36)
Maternal age at delivery (years)			
15 – 19	Reference	Reference	Reference
20 – 39	0.94 (0.91-0.97)	1.01 (0.98-1.04)	1.00 (0.97-1.02)
40 – 50	0.84 (0.81-0.88)	0.93 (0.89-0.97)	0.94 (0.90-0.97)
Birth weight (g)			
Normal (2500 – <4000)	Reference	–	Reference
Fœtal Macrosomia (≥4000)	1.01 (0.98-1.04)	–	0.98 (0.95-1.01)
Low (1500 – <2500)	1.03 (1.01-1.04)	–	0.99 (0.98-1.01)
Very low (1000 – <1500)	1.02 (0.98-1.07)	–	0.95 (0.92-0.99)
Extremely low (<1000)	1.20 (1.11-1.30)	–	1.10 (1.03-1.17)
Multiple pregnancy	1.07 (1.03-1.12)	–	1.02 (0.98-1.06)
Parity			
0	Reference	–	Reference
1	0.95 (0.93-0.96)	–	0.99 (0.98-1.00)
2	0.91 (0.90-0.93)	–	1.02 (1.00-1.04)
≥3	0.86 (0.83-0.89)	–	1.08 (1.05-1.12)
Birth year			
2013	Reference	–	Reference
2014	0.89 (0.87-0.91)	–	0.90 (0.88-0.92)
2015	0.76 (0.75-0.78)	–	0.78 (0.76-0.79)
2016	0.78 (0.76-0.79)	–	0.79 (0.78-0.81)
2017	0.49 (0.48-0.50)	–	0.50 (0.49-0.51)
2018	0.38 (0.37-0.38)	–	0.39 (0.38-0.40)
Maternal death before child age 2 years	1.19 (1.11-1.27)	–	1.07 (1.01-1.14)
Variance of random effect (95% CI): Suburb type	-	0.05 (0.04-0.08)	0.05 (0.04-0.07)
Variance of random effect (95% CI): Suburb type > child ID	–	0.24 (0.23-0.25)	0.14 (0.13-0.14)

[¥]The number of missed well child visits was calculated as the number of visits a child was eligible for (depending on their follow-up time) minus number of visits attended

[†]Mothers who had evidence of starting ART before or during pregnancy, but no electronic evidence of ART dispensing during pregnancy

Variance for child identifier as a random effect in the univariate models is not shown as the variance differs for every univariate model. Models A and B include potential confounders (maternal age and suburb of residence). Model B additionally includes other factors associated with missed well-child visits.
Abbreviations – aIRR: adjusted incidence rate ratio; ART – antiretroviral therapy; CI: confidence interval; g: grams, HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected

Table 6.8: Poisson regression models assessing associations with number of missed well child visits[¥] in HEU children, born in 2017 and 2018, up to age 2 years

	Unadjusted models	Model A	Model B
	uIRR (95%CI)	**aIRR (95%CI) (N=28,536)**	**aIRR (95%CI) (N=28,430)**
Maternal ART engagement			
ART start before pregnancy – no gaps	Reference	Reference	Reference
ART start before pregnancy – gaps	1.37 (1.32-1.43)	1.35 (1.30-1.40)	1.35 (1.30-1.40)
ART start during pregnancy – no gaps	1.41 (1.35-1.47)	1.37 (1.32-1.43)	1.35 (1.30-1.40)
ART start during pregnancy – gaps	1.46 (1.40-1.53)	1.42 (1.37-1.47)	1.40 (1.35-1.46)
ART start at delivery/ postpartum	1.74 (1.63-1.86)	1.65 (1.56-1.75)	1.64 (1.54-1.75)
Unknown ART[†]	1.39 (1.33-1.45)	1.37 (1.32-1.43)	1.37 (1.32-1.43)
No ART evidence ever	1.71 (1.58-1.84)	1.67 (1.57-1.78)	1.64 (1.53-1.75)
Maternal age at delivery (years)			
15 – 19	Reference	Reference	Reference
20 – 39	0.88 (0.82-0.95)	0.98 (0.92-1.05)	0.98 (0.91-1.05)
40 – 50	0.74 (0.67-0.82)	0.85 (0.78-0.93)	0.85 (0.77-0.93)
Birth weight (g)			
Normal (2500 – <4000)	Reference	–	Reference
Fœtal Macrosomia (≥4000)	0.98 (0.91-1.06)	–	1.02 (0.95-1.09)
Low (1500 – <2500)	1.05 (1.01-1.09)	–	1.02 (0.99-1.06)
Very low (1000 – <1500)	1.09 (0.99-1.21)	–	1.04 (0.95-1.15)
Extremely low (<1000)	1.63 (1.35-1.96)	–	1.56 (1.32-1.84)
Multiple pregnancy	1.07 (0.97-1.19)	–	1.03 (0.94-1.13)
Parity			
0	Reference	–	Reference
1	0.93 (0.90-0.95)	–	0.98 (0.96-1.01)
2	0.95 (0.92-0.99)	–	1.02 (0.98-1.06)
≥3	1.02 (0.96-1.09)	–	1.11 (1.05-1.18)
Birth year			
2017	Reference	–	Reference
2018	0.72 (0.71-0.75)	–	0.72 (0.70-0.74)
Maternal death before child age 2 years	1.13 (0.94-1.35)	–	1.06 (0.90-1.26)
Variance of random effect (95% CI): Suburb type	–	0.16 (0.11-0.23)	0.14 (0.10-1.21)
Variance of random effect (95% CI): Suburb type > child ID	–	0.70 (0.67-0.73)	0.68 (0.65-0.70)

[¥] The number of missed well child visits was calculated as the number of visits a child was eligible for (depending on their follow-up time) – number of visits attended

[†] Mothers who had evidence of starting ART before or during pregnancy, but no electronic evidence of ART dispensing during pregnancy

Models A and B include potential confounders (maternal age and suburb of residence). Model B additionally includes other potential factors associated with missed well-child visits.

Abbreviations – aIRR: adjusted incidence rate ratio; ART – antiretroviral therapy; CI: confidence interval; g: grams, HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected

6.5. Discussion

These analyses found that, even when restricting to the most recent calendar years (children born in 2017 or 2018) when electronic capture of data are likely to be most complete, well-child visit coverage is suboptimal for children HEU and HUU with better coverage among children HEU strongly associated with maternal HIV VTP engagement (earlier maternal ART start without gaps). This suggests that societal and healthcare interventions that support maternal engagement in VTP are important for improving well-child visit coverage.

Visit attendance coverage reported for children born in 2017 and 2018 is likely a better reflection of the true population coverage as the electronic capture of routine healthcare data was more complete in these years. For children born between 2013 and 2018, the proportion of children HEU with a visit at each of the observed time-points was low irrespective of maternal ART initiation and adherence. Digital capture within the WCPHDC improved substantially from 2013 onwards; the low coverage of well-child visit attendance when including children born in the earlier years in the analyses may therefore be due to limited electronic data coverage. Although still suboptimal, when restricting to children born in 2017 and 2018, visit coverage was higher than when including children born from 2013, and the most attended visit, among children HEU, was at age 10 weeks. Among children HEU, visit coverage was the highest for children whose mothers started ART before pregnancy, with no gaps, with a coverage of >70% for the 10 week to 18 month visits. Visit coverage was progressively lower for children of mothers with gaps in ART and starting ART during pregnancy or at delivery/postpartum. Visit coverage was lower among children HUU compared to HEU; a higher proportion of children HUU vs. HEU missing all seven visits (31% vs 20%) suggests that there are more children HUU for whom there is no electronic data. Children HEU, are more likely to have digital records as their mothers have at minimum a digital record of their HIV diagnosis.

Based on the recorded data, 83% of children HEU born between 2013 and 2018 appear to have missed ≥1 visit between birth and 2 years of age. The proportion of children missing ≥1 visits is higher than the 59% reported by Ngandu *et al.* in a nationwide SA study conducted between 2012 and 2014 (204). Furthermore, visit attendance coverage at the 18 month time

point in my analysis (50%) was lower than that observed by Ngandu *et al.* (69%); the coverage observed in my analysis was, however, more similar (64%) when restricting to children born in 2017 and 2018. A major difference in their study was that visits were scheduled study follow-ups for which inconvenience allowances were paid. It's also likely that not all visits were electronically recorded in the WCPHDC, particularly in the earlier years. The visit coverage at the 6-week visit (for all HEU children born between 2013 and 2018) in my analysis (57%) may be under-reported, particularly as studies, amongst children born in the WC prior to 2017, have reported high coverage (>77%) of HIV PCR testing of HEU infants at ages 6 and 10 weeks (167,168). Besides poor digital capture in the earlier years, this under-reporting may partly be because high risk birth infants are likely to remain in hospital for an extended period of time and would then not have a separate 6-week encounter as an outpatient.

Children whose mothers initiated ART before pregnancy, and remained in care with uninterrupted ART during pregnancy, had the highest completion of well-child visits. This is in concordance with the findings of Phillips *et al*., in which mothers who disengaged in ART care before pregnancy were more likely to disengage in postpartum care compared to mothers on ART at conception without prior disengagement (208). Although not specific to maternal HIV care, other studies have shown that people living with HIV that disengage and return to care are likely to have future gaps in care (209–211). Furthermore, it's likely that women who have less access to healthcare for themselves will access care in a similar manner for their children (168), which could then reflect as lower attendance at well-child visits. It is possible that the barriers causing their disengagement from healthcare in the first instance (e.g. poverty, remote location, stigma, difficulty accessing health facilities) persist in having the same effect later on (211). Women who initiate ART before pregnancy and remain in care may have more resources to access care, an established healthcare routine and/or be more aware of the importance of consistent healthcare, enabling them to carry out the same for their children.

Compared to children whose mothers started ART before pregnancy with no gaps, those whose mothers started ART during pregnancy, regardless of whether they experienced ART gaps, had higher rates of missed well-child visits. Studies have shown that ART start during

pregnancy (vs. when not pregnant) is associated with subsequent disengagement from care (208,212). Phillips *et al.* reported that 40% of mothers starting ART for the first time during pregnancy had disengaged from treatment by 2 years postpartum (208). Although the proportion of mothers with HIV first evidence date and initiating ART before pregnancy has increased since the introduction of Universal ART in 2016 (208,213), routine HIV testing during antenatal care remains a key entry point into the HIV care continuum (214). An unexpected HIV diagnosis during pregnancy can result in major psychological distress for mothers which could impact ART initiation and continued engagement in care (214). Additionally, mothers will be faced with the challenges of new motherhood, HIV-related stigma, and maintaining HIV treatment (212). Furthermore, in the era of Universal ART, women who are first diagnosed and/or start ART in pregnancy are those who have likely not accessed care or HIV testing except through an antenatal care program and may have worse access to care overall compared to people who start ART when they are not pregnant. These challenges may limit their capacity to ensure their child's well-child visit attendance needs are met.

Children born to mothers who initiated ART at delivery or postpartum had the lowest well-child visit attendance and the greatest increased rate of missed well-child visits (of those whose mothers had electronic records of ART dispensing) compared to children of mothers starting ART before pregnancy with no ART gaps. These results concur with studies that have reported no/limited antenatal care attendance as predictors of not accessing early infant diagnosis testing (168) and incomplete vaccination status among SA children aged 12 -13 months (190). It is possible that the late HIV diagnosis and/or ART initiation among this group of women is reflective of less access to care. I did not have non-HIV antenatal care data for this analysis and this finding therefore requires further investigation but, as suggested above, lower use of antenatal services predicts lower use of services on behalf of children.

As discussed in Chapter 5, mothers with no electronic record in the WCPHDC of ART dispensing ever may be accessing healthcare in the private sector, may have relocated to another province, or may be deceased; in turn coverage of well-child visits is lowest among this group of children HEU. Mothers coded as having unknown ART status in this study had an ART start date before or during pregnancy, but no electronic record of ART dispensing

during pregnancy. It's possible that some of these mothers received ART at facilities that don't report to the WCPHDC, while other mothers were truly not engaged in care. Well-child visit coverage among these children HEU is therefore more in line with that of children HEU who mothers started ART during pregnancy and had an electronic record of ART dispensing.

Maternal age of 40 – 50 years, compared to 15 – 19 years, was associated with a reduced rate of missed well-child visits, with this association being attenuated but persisting after adjustment for maternal ART status. This is in line with other studies (204,208,215,216) and suggests that interventions should especially target younger mothers. Maternal in-hospital death before child age 2 years was associated with an increased rate of missed well-child visits. Maternal death is detrimental to both child survival and the health of orphaned children (217,218). The factors associated with maternal death (e.g. social vulnerability) may in turn be associated with less access to care for mother (prior to death) and child (prior to and post maternal death). Additionally, children with deceased mothers are often separated from their immediate family members, and care, including healthcare use, is dependent on the involvement of their new guardian who is also likely to be under additional financial and other strain (218). Furthermore, there may be increased mobility of these children who may move between guardians. These are a vulnerable group of children whose families require additional cross-sectoral support to ensure their health needs are met (218).

The finding of extremely low birth weight, vs. normal birth weight, being a risk factor for missed well-child visits needs to be considered with caution. Although extremely low birth weight children may have a higher rate of missed visits due to reasons associated with their low birth weight, e.g. poor maternal health, there are other possible explanations for this result. In the WC public healthcare setting, preterm infants who are <35 weeks gestation and <1800g are admitted to neonatal units where they are monitored for potential infections. Infants are only discharged from hospital if they are deemed well, feeding adequately and gaining sufficient daily weight, with provision of kangaroo mother care (intervention for low birth weight infants consisting of skin-to-skin contact between mothers and infants and exclusive breastfeeding) recommended (219). Extremely low birth weight infants may therefore not have primary healthcare encounters for the initial out-of-hospital well-child visits. Furthermore, very low birth weight infants are at greater risk of death and may die out

of hospital with their deaths not being recorded in the WCPHDC (220). This would result in their proportion of missed visits being overestimated.

Strategies that promote and support earlier maternal ART initiation, and sustained engagement in healthcare before, during and after pregnancy could positively impact engagement in well-child services, with the potential to improve child health outcomes including reduced infectious disease hospital admissions (Chapter 5). There are a complex network of factors that impact women's engagement in HIV VTP services (212,221), including individual-level barriers (e.g. education), community-level barriers (e.g. stigma), and health system level barriers (e.g. accessibility of facilities) which need to be considered (222). Results of these analyses suggest that interventions should not be limited to women with HIV and their children, but rather focused on vulnerable groups within the whole of society.

Firstly, there is a need for interventions to support digital capture of healthcare data and to be able to track child engagement across provinces so the extent of their engagement can be more accurately measured. Only through well tracked and captured child care engagement can interventions be targeted to groups that need them most. A Ugandan study has reported the ability of Electronic Medical Records in combination with same day patient tracing to reduce missed clinic visits and loss to follow up amongst patients in a community-based HIV clinic (223).

Socioeconomic status is an important determinant of immunisation uptake in children and is likely to be the same for child healthcare attendance in general (190,224). Lack of transport to clinics and finding time for appointments amongst busy schedules are often reported amongst parents of lower socioeconomic status (224). Community-orientated primary care is one potential measure that could help address socioeconomic status related barriers to healthcare. Community-orientated primary care enables the delivery of childhood services into communities (224,225). Examples of community-orientated care include mobile clinics and home visits. This is particularly helpful in rural populations where access to health facilities is challenging. Community-orientated interventions targeted towards child development and/or health have been effective in several countries (225). Another measure that could assist in reducing barriers due to social inequality is improved and timely access

to childcare grants. Childcare grants play an important role in improving child health outcomes but delays in obtaining these grants deny mothers and children the support they need at a crucial age (226). Mothers often have to return to work prematurely, resulting in them likely neglecting child attendance at well-child visits. Improving health service accessibility is also essential to improving engagement in care.

One suggestion by Phillips *et al.* for improved maternal engagement is the use of differentiated services delivery models to support those at risk of disengagement (208). An example of a differentiated model would be postnatal clubs which offer integrated HIV, maternal and child healthcare services (227). Integrating services into postnatal clubs has shown improved retention of mothers with HIV and children HEU in postnatal care, as well as high infant HIV testing and immunisation rates (227). The postnatal club model has since been adopted into national VTP guidelines (228), but further research is required to identify strategies to successfully facilitate scale-up of the model, and adapt it to accommodate mothers living without HIV (229).

Strengths and limitations

A strength of these analyses is the ability of the WCPHDC to link maternal and child health data and furthermore, link individual data from public sector facilities across the WC, using a unique identifier (148). This enabled me to access maternal and child healthcare data, despite potential within-province transfers between facilities. Conversely, I was not able to account for out-of-province transfers and out-of-hospital deaths, which would likely have resulted in the overestimation of maternal disengagement in care and missed-well child visits. Women with a prior out-of-province ART history may also have been incorrectly classified as having started ART at a later stage in pregnancy (208). Furthermore, my coding of pregnancy start as ≥42 weeks before child date of birth assumes that all pregnancies ran until term, yet >15% of children weighed <2500g grams at birth, of which many were likely preterm. This may also have resulted in the misclassification of the timing of maternal ART start as during pregnancy rather than before pregnancy. An additional limitation is that I did not take into account that women may collect their ART prescription in advance of their current prescription running out and a gap in ART dispensing may be because they had

surplus ART in hand. It was, however, not possible to distinguish early ART collection from those that were because women had run out of ART for other possible reasons (e.g. sharing, loss or theft of ART).

Another limitation is that I did not have data on the reason for child encounters and used timing of the encounter, relative to child age, as a proxy for well-child visits. It's therefore possible that encounters may have been for reasons other than a well-child visit, e.g. if a child was unwell. To limit this misclassification, I excluded hospitalisation encounters and included only primary healthcare visits. It is however possible that children may have had their immunisations and well-child checks done during hospitalisation if it was at the time of a recommended visit, resulting in underestimated coverage of well child visits.

Additionally, with digital capture within the WCPHDC improving substantially from 2013 onwards, child encounters would have been better captured in the later years. This was evident in the adjusted Poisson regression results, with later birth years (compared to 2013) being associated with a reduced rate of missed visits. Because I cannot distinguish actual missed visits from those just not digitally recorded, factors associated with missed visits will, to an extent, also be factors associated with not having a recorded visit. It is also possible that individuals with well captured electronic data in one domain (e.g. maternal ART) also have well captured data in other domains (e.g. child encounters) and therefore those with better maternal engagement seemingly have better well-child healthcare engagement. This analysis may therefore more accurately be considered to represent the association between digitally recorded maternal engagement in VTP services and digitally recorded well-child visits. Suboptimal electronic capture in the earlier years also likely explains why the observed well-child visit coverage is lower than the reported 2016/2017 immunisation coverage of 75%, at age 12 months, among children in the WC (108). To account for poor electronic capture in the earlier years, I reported coverage of well-child visits and carried out Poisson regression models for children born in 2017 and 2018 only. In line with improved electronic capture, well-child visit coverage was higher when restricting to children born in 2017 and 2018. Furthermore, regression outputs for children born only in 2017 and 2018, showed that maternal ART engagement remained associated with missed-well child visits.

I also acknowledge that I did not assess engagement in care amongst children CWH. These are a high risk group for poorer access to care; excluding them on the date of their last negative test may have introduced selection bias, particularly among children HEU, resulting in slight overestimation of well-child visit coverage at later timepoints. However, the proportion of children HEU diagnosed with HIV in this cohort was low (0.5%) and was therefore unlikely to substantially impact observed results.

Conclusions

This population-level analysis highlights an important link between maternal HIV VTP engagement during pregnancy and postnatal well-child healthcare engagement. Coverage of well-child visits was highest among children HEU whose mothers initiated ART before, and remained engaged throughout, pregnancy, and lowest among mothers who initiated ART at delivery or postpartum. Visit attendance completion among children HUU was also suboptimal. This suggests the need for interventions to be focussed on improving well-child healthcare engagement among all infants. These results also highlight that there is a need for interventions to support digital capture of healthcare data, so that maternal and child healthcare engagement can be tracked and interventions targeted to the most vulnerable groups. Further research is required to assess whether more complete well-child visit attendance, among mothers engaged in HIV VTP services, could help mitigate some of the increased risk of infectious disease morbidity, among children HEU vs. HUU, observed in Chapter 5.

CHAPTER 7. DISCUSSION

7.1. Introduction

To date, research has indicated that there are health disparities between children HEU and their HUU counterparts. Although literature predating the Option B+ era (before 2013) suggested an increased risk of infection-related morbidity among children HEU vs. HUU, the evidence was inconclusive due to inconsistent study results (Chapter 1– section 1.2.4). Studies conducted during the Option B+ and Universal ART eras reported that, despite updated guidelines, the increased risk of infectious morbidity remains among children HEU, but that child vaccination, timely maternal ART initiation and optimal breastfeeding mitigated some of the risk difference between children HEU and children HUU (Chapter 1 – section 1.2.5). Children HEU have also been reported to have more severe infectious morbidity compared to children HUU (Chapter 1 – section 1.2.6.1).

The limitations in this field of research that were highlighted in the literature review in Chapter 1 (section 1.2.7), and that have contributed to inconsistent results across studies, included:

- Insufficient controlling for confounders or factors that differ between children HEU and HUU
- Small sample sizes limiting the statistical power of studies to observe differences between groups
- The collection of data at a single healthcare facility limiting the generalisability of study findings
- Potential misclassification of child HIV exposure and infection status and lack of use of standardised classification definitions limiting study comparability
- Few studies in the current Universal ART era, particularly with mothers being able to initiate ART prior to conception, regardless of their CD4 cell count

The literature also highlighted the need for routine-care health data platforms, which could be used to answer important research questions and facilitate evidence-based targeted interventions and policy changes.

The overarching aim of the research presented in this dissertation was to assess whether the burden of infectious disease morbidity differs by *in utero* HIV exposure status in an era of Universal access to ART for all people and recommended prolonged breastfeeding up to age 24 months. This research utilised routine maternal and child healthcare data from the WCPHDC, providing a unique opportunity to assess the real-world impact of the HIV epidemic on child health and health service utilisation. The thesis was structured as follows:

- **Chapter 1** - The literature review chapter provided an overview of: maternal antiretroviral and breastfeeding guideline changes overtime; evidence on infectious disease mortality and morbidity during the Pre-Option B+, Option B+ and Universal ART eras; risk factors for mortality and morbidity in children HEU vs. HUU; and limitations in this field of research.

- **Chapter 2** provided a description of the data source, population setting, study participants, data management, and defining of key variables used in subsequent analyses chapters.

- **Chapter 3** focused on the classification of child *in utero* HIV exposure and infection status, which was then applied to all three other analyses chapters.

- **Chapter 4** described the temporal trends in HIV-related characteristics among children hospitalised for infectious diseases.

- **Chapter 5** evaluated whether there was an increased risk of infection-related hospital admission among children HEU (by maternal ART status) compared to children HUU.

- **Chapter 6** examined whether there is an association between maternal engagement in HIV VTP services and subsequent paediatric healthcare utilisation in the form of well-child visits.

An in-depth discussion was completed in each results chapter (Chapters 3 – 6). This discussion chapter provides a brief summary of the key findings of this research (Section 7.2) and discusses the strengths and limitations, future research, and recommendations for policy and practice in sections 7.3, 7.4, and 7.5 respectively.

7.2. Summary of key findings

7.2.1. Child *in utero* HIV exposure and infection status

I used a simplified version of standardised definitions proposed by The DECIPHER Project to retrospectively classify *in utero* child HIV exposure and HIV infection status at ages one and three years and at the time of first infectious disease hospitalisation, among children born in WC public health facilities between 2008 and 2018 (Chapter 3). The definitions were simplified so that they could be applied to routine data. Among children classified as HEU, 64%, 64% and 90% could be classified with moderate or high certainty at ages one year, three years and at time of hospitalisation respectively. The results of this chapter show that, although designed mainly for prospective use, the standardised child *in utero* HIV exposure definitions proposed by DECIPHER are also retrospectively applicable to routine, linked mother-child data. This supports the results of DECIPHER's evaluation of the applicability of their definitions to the SMARTT cohort (137). The successful application of these definitions to my dataset enabled me to utilise them for the classification of *in utero* HIV exposure and infection status in Chapters 4 – 6, and particularly to perform sensitivity analyses restricted to children classified with high or moderate certainty in Chapter 5.

7.2.2. The HIV-related profile of children with infectious disease hospital admissions

In Chapter 4, I found that, in the context of the scale-up of HIV VTP, there has been a change over time in the HIV-specific profile of children with infection-related hospitalisations, similar to that observed in the general population of children in SA and the WC. There was a reduction in the proportion of CWH from 7% in 2008 to 1.3% in 2018 among children

hospitalised with an infectious disease ≤ age 3 years, and a corresponding increase in children HEU from 14% in 2008 to 17% in 2018. As discussed in Chapter 4, the reduction in the proportion of hospitalised CWH is in line with results reported by Meyers *et al.* (176). Furthermore, among HIV-exposed children there was an increase in the proportion of mothers with HIV evidence before pregnancy start (from 20% in 2008 to 69% in 2021) and starting ART before pregnancy start (from 6% in 2008 to 59% in 2021), among hospitalised children. These results are in line with the introduction of Universal ART in 2016 as mothers no longer had to meet CD4 criteria (i.e. be severely ill) to initiate ART before pregnancy start; this would have likely also motivated for more proactive HIV testing to identify non-pregnant women living with HIV before they became symptomatic. The proportion of mothers with CD4 count <350 cells/µL (recorded closest to delivery) decreased from 91% (2008) to 28% (2021) among hospitalised children HEU, suggesting that ART has improved maternal health.

The temporal trends in HIV-related characteristics, among children with infectious disease hospitalisations, observed in Chapter 4, speaks to the success of the HIV VTP programme in SA; particularly the positive impact increased access to ART has had on reducing vertical HIV transmission and improving maternal health.

7.2.3. Infectious-cause hospitalisation rates, causes and associated factors

In Chapter 5, I observed that children HEU vs. those HUU are at higher risk of infectious-cause hospitalisation in the first year of life, regardless of maternal ART exposure. When stratifying children HEU by timing of maternal ART start relative to estimated pregnancy start, the unadjusted[g] risk of hospitalisation during the neonatal period was 27-50% greater in children HEU, compared to HUU, irrespective of maternal ART. This result is similar to what was reported by Le Roux *et al.*(17). During the postneonatal period, all HEU/ART

[g] Although the lack of adjusting for important confounders was noted as a key limitation of studies in the literature review (Chapter 1), the nature of the data used in this research (i.e. large data size but limited data on confounders) provided the opportunity to report on associations that are in line with the true burden of HIV/ART exposure on infectious disease outcomes in children, rather than assessing causality. I therefore focus here on the unadjusted associations reported in Chapter 5.

exposure groups remained at increased risk of hospitalisation compared to children HUU, however, there was substantial attenuation in the excess risk of admission from the neonatal period (uIRR=1.41; 95% CI: 1.24-1.60) to the postneonatal period (uIRR=1.06; 95% CI: 1.01-1.11) among children HEU (vs. HUU) whose mothers started ART during pregnancy. One hypothesis was that ART start during pregnancy was an indication of engagement in care during the antenatal period which, in turn, may be associated with better engagement in postnatal pediatric care (168,190) and ultimately reduce excess morbidity in children HEU compared to HUU. The observed high excess risk of hospitalisation in the first year of life among children whose mothers restarted ART during pregnancy (uIRR=1.56, 95% CI:1.11-2.20 (neonatal period); uIRR=1.47, 95% CI:1.31-1.66 (postneonatal period)) or weren't on ART during pregnancy (uIRR=1.87, 95% CI:1.34-2.62 (neonatal period); uIRR=1.78, 95% CI:1.58-2.00 (postneonatal period)) vs. children HUU, especially when restricting analyses to children classified HEU or HUU with moderate or high certainty, highlighted the importance of initiating and sustaining ART.

The results of Chapter 5 also showed that, after 12 months of age, children whose mothers started ART before pregnancy and during Universal ART or during pregnancy had a reduced risk of infectious disease hospitalisation compared to children HUU before controlling for potential confounders (uIRR=0.79, 95% CI: 0.63-0.98 and uIRR=0.78, 95%CI: 0.73-0.83 respectively). Evidence from other studies shows that the excess risk of hospitalisation in children HEU vs. HUU wanes with age, however, studies have not stratified HIV exposure by timing of ART start (9,17).

7.2.4. Maternal and paediatric engagement in healthcare

Chapter 6 showed the value of improved electronic data capture of well-child visits. Although even in the most recent years (children born 2017-2018), coverage of well-child visits as captured electronically was suboptimal, it was considerably higher than recorded coverage in earlier years, likely mainly due to expansion of digital health platforms and improved capture.

Among children HEU, attendance of well-child visits differed by maternal engagement in VTP care (timing of maternal ART initiation and consistency in engagement in ART services during pregnancy). This chapter's results showed that the most complete well-child visit attendance was among children HEU whose mothers started ART before pregnancy and remained in care with uninterrupted ART during pregnancy: these children had a 37 to 71% lower rate of missed well child visits compared to those with less thorough maternal VTP engagement (amongst children born 2017-2018). These findings are supported by studies that show that people living with HIV who disengage and return to care and mothers who start ART during pregnancy are likely to subsequently disengage from care (208–212). In my analyses, children HEU whose mothers started ART at delivery/postpartum had the lowest well-child visit attendance. Other studies have also reported no/limited access to antenatal care as a predictor of sub-optimal pediatric healthcare utilisation (168,190).

7.3. Strengths and limitations

7.3.1. Strengths

A major strength of this PhD research was the use of harmonised routine healthcare data maintained and housed within the WCPHDC. The use of linked maternal and child health data from multiple data sources (within the WC and SA) and public health facilities (within the WC) presented an opportunity to investigate infectious disease related health outcomes and child engagement in care, by HIV exposure status, at a provincial population level. Additionally, the use of a unique patient identifier across facilities in the province meant that healthcare use could be tracked across facilities. The linkage of child health data with maternal data pre-pregnancy, during pregnancy and postnatally, enabled the retrospective follow up of a large cohort (N=549,782) of mother-child pairs over a 14 year period. This would not have been feasible for a prospective cohort study collecting data for only research purposes.

Furthermore, the sample size of the provincial dataset used for this research provided sufficient power to stratify HIV exposure status by maternal ART start, enabling the

comparison of HIV/ART exposure in children HEU to those HUU. I was also able to compare infectious disease admission risk by child HIV/ART exposure status for discrete time periods within the neonatal period. The large sample, also enabled the stratification of maternal engagement in VTP services by ART start date and gaps in ART, allowing for a more granular assessment of the association between maternal and paediatric engagement in healthcare. Not only has this research provided real-world insight into what it means to be born to women living with HIV in the WC province of SA and how this compares to children born to women not living with HIV, it has also demonstrated the power of large routine health data repositories to answer important research questions (230).

Another strength of this research is that I was able to retrospectively apply a simplified version of DECIPHER's standardised HIV exposure classification definitions to my dataset. This helps provide transparency around potential HIV exposure misclassification in this research, thereby informing the interpretation and comparability of study results.

Finally, the study period under analysis in this research included the Universal ART period (under current guidelines) in which there was an increasing proportion of mothers starting ART before conception. Very few studies had previously looked at the association between HIV/ART exposure with infectious disease outcomes amongst children born in the Universal ART period. This research therefore contributes to an improved understanding of the health outcomes of children HEU during a period of potential early exposure to ART (regardless of the mother's severity of HIV).

7.3.2. Limitations

This research has several important limitations which need to be acknowledged. The limitations relevant to each analysis chapter have previously been discussed in respective chapters. This section discusses the overarching limitations of this PhD research which may be applicable to one or more chapters.

7.3.2.1. Working with routine health data

Besides the many strengths of working with large scale routinely collected health data, there are limitations to be considered.

Data quality:

Data would have been routinely collected by overburdened healthcare staff, so it is possible that there are data capturing errors. Furthermore, there are different requirements for the completeness and quality of routine healthcare data capture – e.g. hospital admissions are captured in detail with ICD10 codes and discharge summaries etc., while primary healthcare visits are only captured as headcounts. However, as described in Chapter 2, section 2.5, I did work closely with a data analyst at the WCPHDC to resolve data errors arising from data management within the WCPHDC.

Digitisation of data:

Furthermore, the electronic patient administrative system, with a unique identifier, in public-sector facilities within the WC was progressively implemented over time with complete coverage of facilities with patient registration systems only being achieved in October 2017 (148). This means that there were likely missing electronic records in the earlier years of this research. In the earlier years, there would have been a higher proportion of facilities based in rural areas that were not yet part of the electronic patient administrative system. As the antenatal HIV prevalence is lower in the more inland (rural) districts of the WC, compared to the metropolitan region (58), it is possible that the proportion of children with HIV or HEU in my sample in the earlier years overestimated the true population proportion in the WC. Results of this research may therefore be more generalisable to the metropolitan region of the WC, as opposed to the entire province.

Missing electronic infant HIV-PCR test records in the earlier years would have resulted in potential misclassification of HIV exposure and infection status. Classification and ascertainment of hospitalisation records also improved in the later years and as a result, a large proportion of admissions included in my analyses were from 2015 onwards.

Additionally, it was not possible to distinguish between missed well-child-visits and those not electronically recorded. Consequently, poor electronic coverage in the earlier years would have resulted in a seemingly low well-child visit coverage (Chapter 6). These limitations have been acknowledged in their relevant chapter with additional analyses restricted to later study years.

Misclassification:

Rapid point-of-care HIV test results have only recently been digitised in the WC for a small proportion of mothers and children and were therefore not available. I therefore didn't have HIV test results for most mothers and had to assume that mothers with no evidence of living with HIV didn't have HIV. Consequently, most children HUU were classified with low certainty as being HIV-unexposed and the proportion of children HEU may have been underestimated. This would lead to my estimates of the association between HIV exposure and infectious disease outcome being under-estimates of the truth. Antenatal HIV testing rates are, however, high (>95%) in the WC (166) and the WCPHDC would likely have evidence (ART dispensed or CD4 test results) of a mother having HIV had they tested positive. Efforts are underway in the WCPHDC to digitise point-of-care HIV test results.

Another limitation is that cause of hospital admissions was classified using only ICD-10 codes. The accuracy and completeness of ICD-10 codes has previously been reported to be poor (184), and would have particularly affected the earlier years of the study period. There is potential misclassification in the cause of hospitalisation as well as underreporting of infectious-cause admissions. Children may then have been misclassified as not having an infectious-cause hospital admission when they did. There is no evidence regarding whether these potential misclassifications/under reporting differed by HIV exposure status. If under reporting was differential (e.g. children with HIV may have been more likely to be admitted to higher level hospitals with better electronic recording in the earlier years), the true association between HIV exposure and hospitalisation would have been overestimated. In more recent years, ICD-10 code accuracy and completeness has been improved by the implementation of a standardised discharge summary (185), which has likely improved the identification of infection-related admissions.

Due to the lack of gestational age data (see *data availability* section below), pregnancy start date was estimated as 42 weeks before child date of birth. I, however, acknowledge that there are children that would have been born preterm, particularly in light of the evidence of increased risk of preterm delivery in women with HIV discussed below (*Data availability* section). This would have likely resulted in some misclassification of timing of ART start relative to pregnancy. Mothers with shorter pregnancies might therefore have been classified as "ART start during pregnancy", when true ART start was before pregnancy start (i.e. started ART shortly before conception). There will however be no misclassification of those starting ART before pregnancy. If I hypothesise that those born preterm are more likely to have poorer outcomes (i.e. hospitalisation), then this misclassification may have resulted in overestimation of the association between HIV/ART exposure and infectious-cause hospitalisation for children classified as HEU-ART start during pregnancy (compared to HUU).

A further potential source of misclassification to timing of maternal ART start is if mothers previously received HIV treatment outside of the WC or in early years prior to improved digitisation of healthcare data. These mothers may have been classified as newly starting ART during this study period.

Data availability:

A data availability limitation in this research is the lack of access to the private-sector health data. However, as described in Chapter 2 – section 2.2, three quarters of the WC population attend public-sector health services, including most people affected by HIV and of low-income groups. With the aim of having comparable HEU and HUU study groups, and with the lack of accurate SES data, it would have been most appropriate to exclude private-sector data.

An additional limitation is that my analyses were restricted to variables that are routinely collected in maternal and child care and/or available within the WCPHDC. I was therefore not able to assess the impact of important potential confounding factors such as education and substance abuse. Furthermore, I did not have access to breastfeeding and gestational age data and therefore was not able to assess their roles as potential mediators of the

association between HIV/ART exposure and infectious disease admissions. I could also not assess the modifying effects that HIV may have on the protective effects of breastfeeding. Other potential determinants of infectious diseases which I was not able to assess include: vaccination status, malnutrition, immunisation, water, sanitation and hygiene practices, overcrowding, and number of immunocompromised individuals per household. Additionally, although data on maternal ART regimens, and, to a limited extent, maternal pre- and post-exposure antiretroviral prophylaxis and infant postnatal prophylaxis are available within the WCPHDC, these data are complex as regimens may change during a patient's treatment course, and it would have taken a substantial amount of data management to accurately assign exposure to different antiretrovirals at different periods of conception, pregnancy and post-partum, for which there was insufficient time during the PhD period. As a result of these data availability limitations, it was not possible to assess causality within this research. Below, I briefly discuss what is known about the affects of breastfeeding, preterm delivery, vaccination, maternal ART regimens and infant postnatal prophylaxis on infectious disease hospitalisation, based on literature, and how this relates to this research.

Breastfeeding

Breastmilk contains protective factors which play an important role in protecting children against infections; these include antimicrobial agents, antibodies, cytokines, chemokines, antioxidants and microbiota (231). Recent studies have found breastfeeding to be protective against infection-related admissions amongst all infants and to reduce the excess risk of admissions amongst children HEU vs. HUU (especially if exclusively breastfed for a longer duration of time), but not fully eliminate it (17,23,24). However, a common observation among these three studies, which were conducted in the WC, was that children, especially those HEU, were not breastfed for long durations of time. Wedderburn *et al.* reported that only 13% of children HEU in their cohort were breastfed up to age 6 months, while Le roux *et al.* reported that children HEU received any breastfeeding for a median of 4 months, compared to 9 months in children HUU (17,23). This is despite SA guidelines recommending

that children be exclusively breastfed in the first six months of life and receive any breastfeeding for up to or beyond age 24 months (45,46).

Given that a) mothers living with HIV are likely to breastfeed for a shorter duration of time compared to mothers without HIV and b) breastfeeding offers protection against infection-related admissions, it is possible that breastfeeding mediates the association between maternal HIV exposure and infectious-disease outcomes. Moreover, as discussed in Chapter 1 (section 1.2.6.4), studies have reported potential differences in human milk oligosaccharides in mothers with HIV that may result in less protection against infectious morbidity through breastfeeding in women with HIV compared to women without HIV (125,126). It's therefore possible that maternal HIV is acting as an effect modifier of breastfeeding, thereby reducing it's protective effect among breastfed children HEU. There is evidence of this, from the pre-Option B+ era, in a SA study that reported exclusive breastfeeding vs. non exclusive breastfeeding to be protective against presumed bacterial pneumonia amongst children HUU, but not children HEU (193).

Although I did not have access to breastfeeding data for this research, it is likely that breastfeeding durations were short (as observed in the other WC studies). The associations that I observed between HIV/ART exposure and infection-related hospitalisation are therefore reflective of the real-world association in the context of recommended exclusive breastfeeding, but poor uptake thereof. Furthermore, I would expect that, in this dataset, breastfeeding would be protective against infectious disease hospitalisations as was observed in the above mentioned WC studies, but that breastfed children HEU would still have suboptimal health outcomes compared to breastfed children HUU (17,23,24).

Preterm delivery

Women living with HIV have been reported to be at higher risk of having a preterm birth compared to women not living with HIV (115,118,232,233). Moreover, the risk of infectious morbidity and mortality is higher among infants born preterm, with preterm birth being a leading cause of mortality in children under age 5 years (119,234). As HIV exposure may lead

to an increased risk of preterm delivery, which itself increases predisposition to infectious diseases, it is hypothesised that preterm delivery may mediate the pathway between HIV exposure and infectious disease outcomes among children who are HEU. Although I did not have access to gestational age data for these analyses, other WC studies have shown preterm delivery to be associated with infectious disease outcomes and more strongly so in children HEU compared to HUU (23,24). Preterm delivery could therefore potentially be one of the drivers of the increased risk of hospitalisation that I observed in children HEU vs. HUU, particularly during the neonatal period.

Vaccination

Studies have reported that complete and timely vaccination is protective against infectious disease morbidity (17,23,24). Given that a) maternal HIV status may impact a child's vaccination completion rate through increased or decreased engagement with healthcare services and that b) vaccination completion offers protection against infectious disease hospital admissions, it's possible that child vaccination mediates the association between child HIV exposure status and infectious disease outcomes. Vaccination coverage in SA is not reported by HIV exposure, but studies in the WC comparing hospital admissions in children HEU and HUU have described vaccination coverage. In the study by Anderson *et al*., at 14 weeks, 62 vs. 51% of children HEU and HUU respectively, who had a vaccination record (records were missing for 30% of children), were up to date for all their vaccinations (24). Wedderburn *et al.* reported that in their study, vaccination completion was 98 vs. 99% for children HEU and HUU respectively at age 9 months (23). The two studies were carried out in different regions of the WC (Gugulethu and Paarl respectively) and during different time periods (2017 – 2018 and 2012 – 2015 respectively). As I had no data on vaccination, it is not possible to know what the vaccination uptake would have been in my dataset, but if the higher completion of well child visits amongst children HEU vs. HUU, that was observed in Chapter 6, is a proxy for higher vaccination coverage among children HEU, then it's possible that the association between HIV exposure and infection related hospitalisation was underestimated in my analyses.

Maternal ART regimens

Although ART has played a substantial role in HIV VTP and improving maternal health, the potential associated child adverse health outcomes should not be overlooked. As discussed in Chapter 1 – section 1.2.6.3, studies have reported that mothers on ART are at increased risk of adverse birth outcomes compared to mothers without HIV and that this increased risk may differ by timing of ART start and ART regimen (116–118).

As described in section 7.2.3, in my analyses I observed that children HEU were at increased risk of infectious disease admissions during the first year of life, compared to children HUU, regardless of maternal ART status. The extent of excess risk did however differ based on timing of maternal ART start and continuity. As I didn't have data on the different ART regimens in my dataset, I unfortunately wasn't able to assess the effects of different regimens on infection-related admissions. However, in the Slogrove *et al.* study, which used WCPHDC data on children born in the WC in 2018 and 2019, 7% of mothers starting ART before pregnancy were on a protease inhibitor and/or second-or-higher line ART, compared to 1% of mothers starting ART during pregnancy (116). Whether mothers who restarted ART during pregnancy, in my dataset, were more likely on second-or-higher line or protease-inhibitor-based regimens needs to be further investigated. Dolutegravir-based regimens had not yet been implemented during the study period of this research. With more women starting ART before pregnancy in the current Universal ART era and with the rollout of dolutegravir-based regimens, the long term surveillance of and understanding the adverse affects of *in utero* ART exposure should be a research priority (116,235).

Infant postnatal prophylaxis

I did not have data on infant postnatal prophylaxis in my dataset and thus was not able to a) describe the proportion of children HEU who were and were not exposed to either one/both of HIV antiretroviral prophylaxis or Cotrimoxazole prophylactic treatment (CPT), and b) assess whether the associations between HIV/ART exposure and infectious disease outcomes differed by infant exposure to postnatal HIV antiretroviral prophylaxis or CPT. Cotrimoxazole is an antibiotic known for its benefits of preventing bacterial infections, opportunistic infections, and malaria among children with HIV (236). In the early 2000s, WHO guidelines recommended that all children HEU use CPT, as in some settings the risk for

the vertical transmission of HIV was high and there were delays in early infant diagnosis and subsequent ART treatment (236). Evidence has, however, suggested an increase in the risk of antibiotic resistance and microbiome resistance among children HEU on CPT (236,237). Moreover, randomised controlled trials in Botswana and South Africa have shown that there is no clinical benefit of CPT use among children HEU in non-malarial and low mortality (relative to other high HIV prevalence settings) settings (236,237). Despite this evidence and substantial advances in HIV prevention among children HEU and HIV diagnosis and treatment among children with HIV over the years, guidelines have continued to recommend CPT use among children HEU (up until 2023With the recent change in SA national guidelines to remove routine CPT for all children HEU (238), it will be important to monitor and assess any changes in health outcomes among children HEU going forward.

7.3.2.2. Infectious disease causes

A further limitation is that only four infectious diseases were considered in the classifying of infection-related hospital admissions (section 2.6.3). Other important childhood infections such as pulmonary tuberculosis and sepsis were not included in these analyses. LRTIs (including pneumonia) are a leading cause of morbidity and mortality in SA (6). Moreover, a study by Moore *et al.* reported that amongst SA children aged 1 – 11 months, pulmonary tuberculosis was the second leading cause of pneumonia in both HIV-exposed and HIV-unexposed children (191). Furthermore, neonates are at a high risk of bacterial sepsis, regardless of their HIV-exposure status (239). The results of these analyses may therefore not be generalisable to all childhood infectious diseases burdening the healthcare system in the WC.

7.3.2.3. Transfers out of the WC and out-of-hospital deaths

I was not able to determine if children and/or mothers transferred out of the WC, and could therefore not account for this in analyses. In a previous study in the WC, 9% of mothers with HIV had transferred out of the WC within two years after pregnancy (240). Children whose mothers die may also be more likely to move to live with a caregiver in another province. Given that mothers with HIV are at higher risk of mortality, compared to mothers without HIV, hospital admissions and well-child visits among children HEU may have been

underestimated in this research. In turn, the estimated associations between a) child HIV exposure and infectious-cause hospitalisations, and b) maternal engagement in HIV VTP services and well-child visit attendance may have been underestimated.

Furthermore, I did not have access to data on out-of-hospital deaths and causes thereof; it has previously been estimated that 55% and 50% of children under age 5 deaths, in SA and the WC respectively, occur outside of health facilities (241,242). It's possible that these deaths differed by HIV exposure status and therefore acted as competing risk factors for infectious disease hospitalisations and well-child visits, resulting in their underestimation. If a higher proportions of out-of-hospital deaths occurred among children HEU vs. HUU, the estimated associations between a) child HIV exposure and infectious-cause hospitalisations, and b) maternal engagement in HIV VTP services and well-child visit attendance would have been underestimated. In-hospital death did not differ substantially between children HEU and HUU (Chapter 5, section 5.4.1 and Chapter 6, section 6.4) and was therefore not dealt with as a competing risk.

7.3.2.4. Exclusion of mothers with first evidence of HIV during the postnatal period

An additional limitation is that I excluded women with first evidence of HIV during the postnatal period from all analyses. As their exact date of HIV acquisition is unknown, there is uncertainty surrounding the HIV status of these mothers during pregnancy. Mothers who acquire HIV postnatally are an important group of women whose children are exposed to a high viral load via breastmilk and are at a higher risk of acquiring HIV, compared to children of mothers with chronic HIV (169). It is, however, complex to define HIV exposure in this group of children due to the uncertainty around infant age at maternal postnatal HIV-acquisition and the duration of HIV exposure via breastfeeding. The DECIPHER project has also not yet developed definitions for classifying postnatal HIV exposure. Furthermore, mothers with first HIV evidence during the postnatal period accounted for a relatively small proportion of all HIV exposure in my dataset (<2% of all children with a birth record in the WCPHDC between 2008 and 2018 were born to mothers with first HIV evidence during the postnatal period, compared to 15% of all children with *in utero* HIV exposure).

7.4. Future work

Although this PhD research provides insight into the real-life burden of HIV/ART exposure on the health and healthcare of children HEU in the WC province of SA, further research is required to better understand the vulnerabilities of these children to enable them to survive and thrive. In this section, I discuss future research that has not yet been covered in this discussion chapter.

First, these findings may not be generalisable to other settings. SA is subject to interprovincial health inequalities and heterogeneity in maternal HIV related characteristics (e.g. antenatal HIV prevalence, maternal ART uptake, ART regimen types) across provinces and within provinces (across provincial districts) (58,243). It's therefore important that similar observational studies using routine healthcare data, where feasible, are carried out in different settings including children living in rural and urban/peri-urban communities. Furthermore, as the use of dolutegravir-containing regimens had not yet been rolled out during this research period, it is necessary to repeat these analyses in more recent years to assess these outcomes under current guidelines.

Given that this research did not focus on assessing causality, additional work is required to understand the mechanisms behind the increased risk of infection-related hospitalisation in children HEU vs. HUU. As discussed above (section 7.3.2.1), preterm delivery and breastfeeding can be considered to be on the causal pathway mediating the association between maternal HIV/ART exposure and infectious disease outcomes. In studies with sufficient data on preterm delivery, breastfeeding and confounders, a mediation analysis could be conducted to give insight into the extent to which these mechanisms impact the association between maternal HIV/ART exposure and infectious disease outcomes. This would inform the magnitude of the potential effect of intervening on the mediating mechanism. By intervening on one of the mediator pathways, it may be possible to eliminate a portion of the exposure outcome effect.

While understanding the biological effects of HIV and ART exposure on the health outcomes of children HEU is important, we know that the network of factors affecting children HEU is

complex. A recent publication by Le Roux *et al.* highlighted the syndemic interactions between maternal HIV and intimate partner violence, hazardous drinking and household food security (95). Research that investigates the social and structural elements of suboptimal health among children HEU should therefore be a priority. This may require more focussed measurement in smaller prospective cohorts, but as suggested by Lee *et al.* the integration of both smaller cohort studies and larger routine-data studies could help with the identification of children HEU at highest risk of poor health outcomes (244).

The importance of including women with HIV and children HEU (where possible) as research partners, given their first-hand life experiences, has also been highlighted (245). A family/community-centred approach to research may provide unique insights into the disparities faced by this vulnerable population, thereby guiding research priorities and enhancing the research impact (245,246). Including community members can also empower them to play a more active part in their own healthcare and facilitate implementation of any interventions (246).

Research is required to identify why current policies and/or interventions to improve health outcomes among children are producing suboptimal results. As mentioned by Prendergast and Evans, there are already evidence-based interventions that aim to improve child survival, but the coverage of these interventions is insufficient (247). Another research gap discussed by Prendergast and Evans and Le Roux *et al.* is the lack of trials that have investigated comprehensive multi-component interventions among children HEU up until now (95,247). Multi-component interventions are particularly important given the syndemic vulnerability of children HEU, and would benefit from interdisciplinary collaboration among community members, clinicians, economists, social scientists, epidemiologists, policy makers and programme implementers (244,248). An example of a bundled intervention is that of the SHINE trial that combined two interventions, namely the water sanitation and hygiene (WASH) and the improved infant and young child feeding (ICYF) interventions (249). They found that among HIV-exposed children, combining the interventions improved early developmental outcomes, whereas each intervention alone had no impact on developmental outcomes. Other interventions including cash transfers/child support grants

(250), food support (251), community support groups/mentors (252,253), and postnatal clubs integrating maternal and child healthcare (227) have been shown to positively impact health outcomes in all children irrespective of HIV exposure status (e.g. reduced mortality, improved cognitive function and growth) and adults (reduced mortality).

Given that children were being born HEU from as early mid-late 1980s, the population is ageing into adolescence and early adulthood (244). To date, research has mainly focussed on the health outcomes of children HEU in early life, however, it is essential that the longer term health outcomes of children HEU are also assessed. Due to the syndemic exposures of children HEU, they are likely to continue to be impacted by the social and structural challenges they faced as children affected by HIV. It will also be important to investigate the health outcomes of children born to adolescents and adults who are themselves HEU. Although they will not be directly exposed to HIV and ART, it is possible that they will be exposed to a home environment affected by HIV. Adolescents and adults HEU and their children may therefore need additional multi-component support, in the same way that families of children HEU do. The use of electronic routine care databases, such as the WCPHDC, will help facilitate the long term follow-up of children HEU and their children, who may otherwise be difficult to find and follow. Additions/improvements to the WCPHDC that will be beneficial in the long term follow up of children HEU (but not limited to children HEU) include: improved codeing of reasons for hospital admissions; inclusion of radiology data which will be useful for LRTI diagnosis; improved capture of vaccination data; capture of breastfeeding data; improved coding of malnutrition; inclusion of out-of-facility mortality data; linkage of children to fathers, siblings, and caregivers; inclusion of community surveillance data, e.g. community health worker visits; and the inclusion of data on SES.

Following on from the results observed in Chapter 6 of this PhD research, further studies are required to investigate whether more complete well-child visit attendance is associated with a reduced risk of infectious disease outcomes in children HEU. As mentioned in Chapter 6 – section 6.5, it is however important to first establish more complete electronic digitisation of healthcare data (including well-child visits) to enable more accurate tracking of child care engagements and assessment of their association with child health outcomes.

Finally, going forward the use of standardised HIV exposure and health outcome definitions in studies will allow for more sharable data and transparent and comparable study outputs (137).

7.5. Recommendations for policy and practice

This research has highlighted a) the success of the HIV VTP programme in SA, b) that health outcomes in children HEU are still suboptimal compared to children HUU, and c) maternal engagement in healthcare is associated with paediatric engagement in healthcare among children HEU. As mentioned in the literature review (section 1.2.6) the network of factors proposed to be responsible for the differences in health outcomes between children HEU and HUU is complex and multi-faceted (9). There are factors that are specific to HIV-exposure, e.g. exposure to maternal ART, and factors that are universal to all children, but that may occur more frequently among families affected by HIV, e.g. poor SES. In this section, I describe recommendations for policy and practice with respect to both HIV-specific recommendations and universal recommendations.

The change in HIV-related characteristics among hospitalised children, observed in Chapter 4, emphasised the positive impact of the scale-up of the HIV VTP programme in SA. It, however, also highlighted that there are still children and mothers falling through gaps in the HIV care continuum; children who are diagnosed with HIV, children whose mothers are diagnosed with HIV and/or start ART at delivery/postnatally, and children whose mothers have a HIV viral load of ≥1000 copies/mL and/or CD4 count of <350 cells/μL. In the early 2000s the WHO recommended a four-pronged strategy to eliminate the vertical transmission of HIV (166). These prongs are: 1) preventing new HIV infections in women, 2) preventing unwanted pregnancies in women living with HIV, 3) preventing vertical HIV transmission, 4) treatment and support for families affected by HIV. As suggested by Goga *et al.*, although there has been substantial progress made in prongs three and four, high antenatal HIV prevalence rates will still result in a significant number of children with perinatally acquired HIV, even when vertical transmission rates are low. Additionally, the 2019 antenatal HIV survey reported that 50% of pregnancies among women with HIV in the

WC were unintended (175). A reduction in annual maternal HIV incidence and unintended pregnancies will not only reduce the incidence of perinatal child HIV infections but also the incidence of children HEU. In some instances, mothers become pregnant before knowledge that they are living with HIV. The early diagnoses of HIV and starting of ART in pregnancy is therefore essential and, as noted by Le Roux, this is reliant on early presentation for antenatal care (248). The 2022 Antenatal HIV survey estimated that, in the WC, 72% and 40% of mothers living with HIV attended their first antenatal visit before 20 and 12 weeks gestation, respectively (58). Once mothers are on ART, interventions are required to help maintain their engagement in care, particularly during the postpartum period, as was highlighted in Chapter 6.

Each of the above mentioned steps in the HIV VTP continuum provide opportunities for intervention. Although, there are up and coming innovations (discussed below), there should also be a focus on improving current evidence-based interventions and policies that are already in place and have been proven to work (247). It's important that the effectiveness of current policy interventions is monitored, challenges related to the implementation of the interventions are identified, and interventions are enhanced for optimal benefit. New innovations that are likely to play an important role in closing gaps in the HIV care continuum are long-acting PrEP and long-acting ART. With reduced dosing frequency, both have the potential to help with the challenge of retaining maternal engagement in and adherence to PrEP/ART care (254,255). In turn, long-acting PrEP will assist with preventing HIV in everyone (including pregnant women) (256) and long-acting ART will reduce the rate of vertical HIV transmissions and improve maternal health which will potentially reduce HEU vulnerability (254).

As suggested by the syndemic relationships associated with living with HIV, we need to look beyond just HIV care to optimise maternal and child health among this vulnerable population (248). This is supported by the finding in Chapter 5 that regardless of maternal ART, and its likely association with improved maternal health and reduced exposure to *in utero* HIV levels, children HEU are still at higher risk of infectious disease outcomes compared to children HUU. Factors universally associated with poor health outcomes in all children

including suboptimal breastfeeding, adverse birth outcomes, food insecurity, poor SES, lack of maternal education, child malnutrition, intimate partner violence, and caregivers' mental illness are generally also associated with maternal HIV (12,74,95). Policy interventions that address common universal risk factors of suboptimal child health will benefit both children HEU and HUU.

In 2018, the WHO published The Nurturing Care Framework which is a comprehensive evidence-based roadmap to help children survive, thrive and reach their full potential (257). The framework forms the core for The Global Strategy for Women's, Children's and Adolescent's Health and the Sustainable Development Goals (Figure 7.1). The framework acknowledges that many of the SDGs directly influence the development of children, but that attainment of the SDGs also relies on optimal childhood development. It proposes five components for a whole-of-government and a whole-of society approach to ensure nurturing care for all children (258). These components are "adequate nutrition, responsive caregiving, safety and security, opportunities for early learning and good health". The framework goes on to describe policies and interventions, specific to each of these 5 components, aimed at assisting parents and caregivers to provide the necessary nurturing care for their babies (Figure 7.2). Furthermore, the framework suggests three levels of support for the nurturing care: universal support, targeted support and indicated support (257,258). Universal support is general support for all, regardless of risks, e.g. antenatal care and immunisations. Targeted support would be applicable to children and mothers or families who are at risk of poor outcomes at a later stage because of factors such as HIV, poverty or malnutrition. Indicated support is specialised support for individuals with additional needs e.g. preterm babies. Both targeted and indicated support could be implemented through additional facility-based support, community groups and home visits. This three-tier support system emphasises that all families need support to ensure nurturing care for their children, but that there are high risk groups that require additional support (258). This framework of care is important in children HEU as they are a vulnerable population some of whom likely require additional targeted and indicated support.

Figure 7.1: The Nurturing Care Framework forming the core of the Global strategy and Sustainable Developmental Goals.

Figure Source: Reproduced from World Health Organization, United Nations Children's Fund, World Bank Group (257) Under a CC BY-NC-SA 3.0 license.

	Laws and policies	Services and interventions
Component 1: Good health	**Universal health coverage** This is when everyone gets the good-quality health services they need without suffering financial hardship. It is especially important that caregivers and families are able to access the full range of these services from health facilities and in their communities. These should include promotive and preventive services, as well as treatment, rehabilitation and palliative care.	• Family planning • Immunization for mothers and children • Prevention and cessation of smoking, alcohol and substance use • Prevention of mother-to-child transmission of HIV • Support for caregivers' mental health • Antenatal and childbirth care • Prevention of preterm births • Essential care for new-born babies, with extra care for small and sick babies • Kangaroo care for low-birthweight babies • Support for timely and appropriate care-seeking for sick children • Integrated management of childhood illness • Early detection of disabling conditions (such as problems with sight and hearing) • Care for children with developmental difficulties and disabilities
Component 2: Adequate Nutrition	**The International Code of Marketing of Breast-milk Substitutes, and the accompanying guidance** The inappropriate marketing of food products is an important factor that negatively affects mothers' choice to breastfeed in the best way. There is a Code and guidance on ending this inappropriate promotion of foods for infants and young children. These are important tools for creating an environment that enables mothers to make the best possible feeding choice, based on impartial information and free of commercial influences. And it helps mothers to be fully supported when they make that choice. **Baby-friendly Hospital Initiative (BFHI)** Maternity services play an important role, supporting mothers in bonding with their children through body contact and optimal breastfeeding practices. The services do this supporting mother to put their baby to the breast immediately after birth, not providing water and not allowing formula samples to be distributed. The BFHI's ten steps describe the essential conditions for protecting, promoting and supporting breastfeeding. And the Baby-friendly Community Initiative extends this support for breastfeeding beyond health facilities.	• Maternal nutrition • Support for early initiation, exclusive breastfeeding and continued breastfeeding after 6 months • Support for appropriate complementary feeding and for transition to a healthy family diet • Micronutrient supplementation for mother and child, as needed • Fortification of staple foods • Growth monitoring and promotion, including intervention and referral when indicated • Deworming • Support for appropriate child feeding during illness • Management of moderate and severe malnutrition as well as being overweight or obese

Figure 7.2: Laws, policies, services and interventions that address the five components of the nurturing care framework.

Figure Source: Reproduced from World Health Organization, United Nations Children's Fund, World Bank Group (257) Under a CC BY-NC-SA 3.0 license.

	Laws and policies	Services and interventions
Component 3: Responsive caregiving	**Paid parental leave** Paid parental leave is associated with several health benefits for children. They include supporting the bonding between mother and child, increasing the initiation and duration of breastfeeding, and improving the likelihood of infants' being vaccinated and receiving preventive care. New fathers are more involved with their young children and take on more child-care responsibilities when they take leave from work. **Affordable child-care services** There has been an increase in the number of women in the workforce and therefore, caregivers need affordable, good-quality day care for their children. This is also important for the high numbers of single mothers, and for caregivers or children living with disabilities. **Urban design** This should include green and child-friendly spaces that promote play between caregivers and children, as well as learning.	• Skin-to-skin contact immediately after birth • Kangaroo care for low-birthweight babies • Rooming-in for mothers and young infants, and feeding on demand • Responsive feeding • Interventions that encourage play and communication activities of caregiver with the child • Interventions to promote caregiver sensitivity and responsiveness to children cues • Support for caregivers' mental health • Involving fathers, extended family and other partners • Social support from families, community groups and faith communities
Component 4: Opportunities for early learning	**Universal access to good-quality day care for children, as well as pre-primary and primary education** Developmentally appropriate early education is crucial to children's cognitive and social development, and to their preparation for formal schooling. It is important for children across all demographic groups to have access to tuition-free pre-primary and primary education. This is especially important for children from vulnerable populations, as stress adversely affects children's learning.	• Information, support and counselling about opportunities for early learning, including the use of common household objects and home-made toys • Play, reading and story-telling groups for caregivers and children • Book sharing • Mobile toy and book libraries • Good-quality day care for children, and pre-primary education • Storytelling of elders with children • Using local language in children's daily care
Component 5: Security and safety	**Social protection and social services** Social protection encompasses both insurance and income assistance (such as social grants and pensions) and provides direct, regular and predictable income for poor and vulnerable households. An important and growing part of social welfare in many countries, social assistance provides income security that reduces household poverty, mitigates against shocks, improves access to health and other services, and can increase immunization coverage, improve children's and mothers' health and nutrition, and boost school attendance and achievement. **Minimum wage** When caregivers are not able to earn adequate income, children's basic needs – including health care and education – cannot be met and early childhood development suffers. A minimum wage has the potential to improve the lives of millions of children, whether their caregivers work in the formal or informal economy.	• Birth registration • Provision of safe water and sanitation • Good hygiene practices – at home, at work and in the community • Prevention and reduction of indoor and outdoor air pollution • Clean environments free of hazardous chemicals • Safe family and play spaces in urban and rural areas • Prevention of violence by intimate partners and in families, as well as services for addressing it • Social care services • Cash or in-kind transfers and social insurance • Supporting family care and foster care over institutional care

Figure 7.2 continued.

Although many of the evidence-based interventions for optimal early childhood development suggested by the Nurturing Care Framework are already in place in SA, the coverage and implementation of the interventions has been poor – even when engagement with an intervention is high, it may still not be used optimally, e.g. only attending one out of

eight antenatal care visits (259–261). As emphasised by others, improving the implementations of the interventions already in place should be a priority (247,248,261). In order to do so, monitoring and evaluation is essential to track and measure intervention implementation and coverage (260). Immunisations are an example of an intervention that is already in place, but where recent innovations could improve child health. In the WC, guidelines have been updated to include a combined tetanus, diphtheria and acellular pertussis vaccine during pregnancy and a child rubella vaccine (combined with measles vaccine) as part of the expanded programme on immunisation (EPI) (262). Maternal and/or child immunisation against respiratory syncytial virus (a common cause of LRTIs), although not yet licensed in SA, has been modelled to likely be cost effective in low-and-middle income countries and in the future could play an important role in reducing the burden of LRTIs amongst vulnerable children (263). With the 2020 EPI national coverage survey reporting an immunisation coverage of 84% at age 12 months among children in the WC (264), interventions are required to improve immunisation rates so that all children can benefit from current and future vaccinations.

There have been vast improvements in child health in SA, but these gains are limited by lack of access to public health services, particularly among vulnerable children (259). More efforts are therefore required to ensure that all mothers and children have access to available services and that children that are likely not to have access and that need extra support are identified. Community health workers (CHW) play a key role in bringing the services provided at primary healthcare facilities into homes (259,260). This will assist with providing comprehensive primary care to those that aren't able to access health facilities and also provide additional contact points with healthcare for those identified to be at risk of poor health outcomes. Community health workers are currently placed throughout healthcare clinics in the WC as part of an integrated health and wellness community package providing HIV-related services, family planning, nutrition advice etc. (265). Despite being linked to the healthcare system by policy, CHWs are managed through non-governmental organisations which rely on provincial grant allocations and other funding sources (266). Poor support systems, low remuneration, lack of political commitment, and under resourcing are among challenges faced by CHWs (266). However, as described by Le Roux,

CHW centred models that have been implemented by non-governmental organisations themselves have been successful, particularly when CHWs were mothers (248). Programmes that have implemented these models include the “Goodstart”, the “Philani Maternal, Child Health and Nutrition Trust” and “Mothers2Mothers”; results have included improvements in: antenatal care attendance, rates of exclusive breastfeeding, child growth, child neurodevelopment, and maternal health (266–269). Despite the positive outcomes of these programs, they are not yet universally implemented in SA.

Furthermore, the need for the health sector to shift from a ‘survive’ to a ‘survive and thrive’ approach to healthcare has been noted (260). This would entail the reorganisation of health services, e.g. combining mother and child services to allow for more integrated care, and implementing more child and mother-centred interactions with healthcare providers. It’s important that adequate time is spent on counselling mothers/caregivers about child development, health and nutrition during well-child visits in such a way that empowers them and encourages joint decision making concerning their child’s health (260). At the same time, health workers need to be supported through ongoing education, mentorship, supervision and sufficient resources to enable them to implement a ‘survive and thrive’ approach.

Finally, this PhD research has demonstrated how electronic healthcare data platforms centred around the use of unique patient identifiers across healthcare facilities and the linkage of maternal and child healthcare can be leveraged to monitor health outcomes among children HEU. Not only do these platforms enable the classification of children HEU, they also inform the size of the population of children HEU relative to HUU and allow for the short to long term follow-up of this vulnerable population, with routine care visits, health outcomes and pharmacovigilance (3). Although not yet implemented, similarly to the mobile application described be Le Roux (248), electronic data platforms could use a number of indicators (e.g. low birth weight, maternal healthcare engagement history, hospitalisation records) to flag high risk children HEU who may require additional support from healthcare and social systems (e.g. regular visits from CHWs, assistance in accessing childcare grants, reminders to attend well-child visits etc.). Furthermore, the long term surveillance of children HEU will also enable the identification and monitoring of their children in the future.

Although there would be immense benefit in linking to additional data such as social grant access and national education assessment results, the importance of data governance has to be kept in mind. It is essential to balance accessibility to sensitive healthcare data and privacy (270). In SA, the Protection of Personal Information Act (POPIA) regulates data protection (271). POPIA has eight requirements for the processing of personal data: openness, accountability, purpose specification, processing limitation, further processing limitation, data subject participation, information quality and security safeguards (271). This adds challenges to the sharing of and gaining access to personal health information.

In summary, both HIV-specific and universal interventions, delivered by health services and across society, are necessary to ensure optimal health among children HEU. Evidence-based interventions are already included in health policies, but implementation and coverage of these interventions have been suboptimal. Monitoring, evaluation and improved implementation of these interventions should be a priority. Furthermore, electronic healthcare data platforms enable informative monitoring of children HEU and could assist with identifying children HEU requiring additional support. Targeted interventions, e.g. mother mentoring from CHWs, could then be used to provide HIV affected families with the additional support needed to ensure their children survive and thrive.

7.6. Conclusions

To my knowledge, this thesis presents the largest analyses of infectious disease outcomes among children HEU, compared to HUU, in SA to date. It used routine healthcare data from the WCPHDC to: a) classify child *in utero* HIV exposure and infection status, b) describe the temporal trends in HIV-related characteristics among children hospitalised with infectious diseases over a 14 year period, c) describe the characteristics, causes, rates of, and factors associated with infectious disease hospital admissions, and d) describe the completion of well-child visits, by HIV exposure status and maternal engagement in HIV VTP services.

This thesis concludes with recommendations for future research, policy and practice, all of which aim to contribute towards ensuring that children HEU survive, thrive and are able to strive towards reaching their full potential in life. Although these recommendations were discussed with a focus on children HEU, I acknowledge that optimal health is critical for all children and that there are also vulnerable children HUU who could benefit from interventions that improve health in children HEU. Universal interventions should therefore place equal priority on improving the health outcomes of both children HEU and HUU.

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APPENDICES

Chapter 2 appendix

Classification of infectious disease hospitalisation

Appendix Table 2.1: List of International Classification of Diseases 10th Revision (ICD-10) codes used for classifying infectious disease hospital admissions (156)

ICD-10 code	Description
LRTI	
B01.2	Varicella pneumonia (J17.1*)
B20.6	HIV disease resulting in Pneumocystis jirovecii pneumonia
B25.0	Cytomegaloviral pneumonitis (J17.1*)
B59	Pneumocystosis (J17.3*)
J05	Acute obstructive laryngitis [croup] and epiglottitis
J05.0	Acute obstructive laryngitis [croup]
J05.1	Acute epiglottitis
J05.X	Acute obstructive laryngitis [croup] and epiglottitis
J09	Influenza due to identified zoonotic or pandemic influenza virus
J09.X	Influenza due to certain identified influenza virus
J10	Influenza with other manifestations, other influenza virus identified
J10.0	Influenza with pneumonia, other influenza virus identified
J10.1	Influenza with other respiratory manifestations, other influenza virus identified
J10.8	Influenza with other manifestations, other influenza virus identified
J10.X	Influenza due to other identified influenza virus
J11	Influenza, virus not identified
J11.0	Influenza with pneumonia, virus not identified
J11.1	Influenza with other respiratory manifestations, virus not identified
J11.8	Influenza with other manifestations, virus not identified
J11.X	Influenza, virus not identified
J12	Viral pneumonia, not elsewhere classified
J12.0	Adenoviral pneumonia
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus pneumonia
J12.3	Human metapneumovirus pneumonia
J12.8	Other viral pneumonia
J12.9	Viral pneumonia, unspecified
J12.X	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J13.X	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J14.X	Pneumonia due to Haemophilus influenzae

J15	Bacterial pneumonia, not elsewhere classified
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to Pseudomonas
J15.2	Pneumonia due to Staphylococcus
J15.3	Pneumonia due to Streptococcus, Group B
J15.4	Pneumonia due to other streptococci
J15.5	Pneumonia due to Escherichia coli
J15.6	Pneumonia due to other aerobic Gram-negative bacteria
J15.7	Pneumonia due to Mycoplasma pneumoniae
J15.8	Other bacterial pneumonia
J15.9	Bacterial pneumonia, unspecified
J15.X	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
J16.X	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J17.0	Pneumonia in bacterial diseases classified elsewhere
J17.1	Pneumonia in viral diseases classified elsewhere
J17.2	Pneumonia in mycoses
J17.3	Pneumonia in parasitic diseases
J17.8	Pneumonia in other diseases classified elsewhere
J17.X	Pneumonia in diseases classified elsewhere
J18	Pneumonia, organism unspecified
J18.0	Bronchopneumonia, unspecified
J18.1	Lobar pneumonia, unspecified
J18.2	Hypostatic pneumonia, unspecified
J18.8	Other pneumonia, organism unspecified
J18.9	Pneumonia, unspecified
J18.X	Pneumonia, organism unspecified
J20	Acute bronchitis
J20.0	Acute bronchitis due to Mycoplasma pneumoniae
J20.1	Acute bronchitis due to Haemophilus influenzae
J20.2	Acute bronchitis due to streptococcus
J20.3	Acute bronchitis due to coxsackievirus
J20.4	Acute bronchitis due to parainfluenza virus
J20.5	Acute bronchitis due to respiratory syncytial virus
J20.6	Acute bronchitis due to rhinovirus
J20.7	Acute bronchitis due to echovirus
J20.8	Acute bronchitis due to other specified organisms
J20.9	Acute bronchitis, unspecified
J20.X	Acute bronchitis
J21	Acute bronchiolitis
J21.0	Acute bronchiolitis due to respiratory syncytial virus
J21.1	Acute bronchiolitis due to human metapneumovirus
J21.8	Acute bronchiolitis due to other specified organisms

J21.9	Acute bronchiolitis, unspecified
J21.X	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J22.X	Unspecified acute lower respiratory infection
P23	Congenital pneumonia
P23.0	Congenital pneumonia due to viral agent
P23.1	Congenital pneumonia due to Chlamydia
P23.2	Congenital pneumonia due to staphylococcus
P23.3	Congenital pneumonia due to Streptococcus, Group B
P23.4	Congenital pneumonia due to Escherichia coli
P23.5	Congenital pneumonia due to Pseudomonas
P23.6	Congenital pneumonia due to other bacterial agents
P23.8	Congenital pneumonia due to other organisms
P23.9	Congenital pneumonia, unspecified
Diarrhoea	
A00.9	Cholera, unspecified
A01	Typhoid and paratyphoid fevers
A01.0	Typhoid fever
A01.1	Paratyphoid fever A
A01.2	Paratyphoid fever B
A01.3	Paratyphoid fever C
A01.4	Paratyphoid fever, unspecified
A01.X	Typhoid and paratyphoid fevers
A02	Other salmonella infections
A02.0	Salmonella enteritis
A02.2	Localized salmonella infections
A02.8	Other specified salmonella infections
A02.9	Salmonella infection, unspecified
A03	Shigellosis
A03.0	Shigellosis due to Shigella dysenteriae
A03.1	Shigellosis due to Shigella flexneri
A03.2	Shigellosis due to Shigella boydii
A03.3	Shigellosis due to Shigella sonnei
A03.8	Other Shigellosis
A03.9	Shigellosis, unspecified
A03.X	Shigellosis
A04	Other bacterial intestinal infections
A04.0	Enteropathogenic Escherichia coli infection
A04.1	Enterotoxigenic Escherichia coli infection
A04.2	Enteroinvasive Escherichia coli infection
A04.3	Enterohaemorrhagic Escherichia coli infection
A04.4	Other intestinal Escherichia coli infections
A04.5	Campylobacter enteritis
A04.6	Enteritis due to Yersinia enterocolitica
A04.7	Enterocolitis due to Clostridium difficile
A04.8	Other specified bacterial intestinal infections

A04.9	Bacterial intestinal infection, unspecified
A05	Other bacterial foodborne intoxications, not elsewhere classified
A05.0	Foodborne staphylococcal intoxication
A05.1	Botulism
A05.2	Foodborne Clostridium perfringens [Clostridium welchii] intoxication
A05.3	Foodborne Vibrio parahaemolyticus intoxication
A05.4	Foodborne Bacillus cereus intoxication
A05.8	Other specified bacterial foodborne intoxications
A05.9	Bacterial foodborne intoxication, unspecified
A06	Amoebiasis
A06.0	Acute amoebic dysentery
A06.1	Chronic intestinal amoebiasis
A06.9	Amoebiasis, unspecified
A07	Other protozoal intestinal diseases
A07.0	Balantidiasis
A07.1	Giardiasis [lambliasis]
A07.2	Cryptosporidiosis
A07.3	Isosporiasis
A07.8	Other specified protozoal intestinal diseases
A07.9	Protozoal intestinal disease, unspecified
A08	Viral and other specified intestinal infections
A08.0	Rotaviral enteritis
A08.1	Acute gastroenteropathy due to Norwalk agent
A08.2	Adenoviral enteritis
A08.3	Other viral enteritis
A08.4	Viral intestinal infection, unspecified
A08.5	Other specified intestinal infections
A08.X	Viral and other specified intestinal infections
A09	Other gastroenteritis and colitis of infectious and unspecified origin
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
A09.9	Gastroenteritis and colitis of unspecified origin
A09.X	Other gastroenteritis and colitis of infectious and unspecified origin
K52.3	Indeterminate colitis
R19.7	Diarrhoea, unspecified
Meningitis	
Bacterial meningitis	
A20.3	Plague meningitis
A32.1	Listerial meningitis and meningoencephalitis
A39.0	Meningococcal meningitis (G01*)
G00	Bacterial meningitis, not elsewhere classified
G00.0	Haemophilus meningitis
G00.1	Pneumococcal meningitis
G00.2	Streptococcal meningitis
G00.3	Staphylococcal meningitis
G00.8	Other bacterial meningitis
G00.9	Bacterial meningitis, unspecified

G00.X	Bacterial meningitis, not elsewhere classified
G01	Meningitis in bacterial diseases classified elsewhere
G01.X	Meningitis in bacterial diseases classified elsewhere
Viral meningitis	
A87	Viral meningitis
A87.0	Enteroviral meningitis (G02.0*)
A87.1	Adenoviral meningitis (G02.0*)
A87.2	Lymphocytic choriomeningitis
A87.8	Other viral meningitis
A87.9	Viral meningitis, unspecified
A87.X	Viral meningitis
B00.3	Herpesviral meningitis (G02.0*)
B01.0	Varicella meningitis (G02.0*)
B02.1	Zoster meningitis (G02.0*)
B26.1	Mumps meningitis (G02.0*)
G02.0	Meningitis in viral diseases classified elsewhere
G03.0	Nonpyogenic meningitis
G03.2	Benign recurrent meningitis [Mollaret]
Fungal meningitis	
B37.5	Candidal meningitis (G02.1*)
B38.4	Coccidioidomycosis meningitis (G02.1*)
G02.1	Meningitis in mycoses
Other meningitis	
G02	Meningitis in other infectious and parasitic diseases classified elsewhere
G02.8	Meningitis in other specified infectious and parasitic diseases classified elsewhere
G03	Meningitis due to other and unspecified causes
G03.1	Chronic meningitis
G03.8	Meningitis due to other specified causes
G03.9	Meningitis, unspecified
G03.X	Meningitis due to other and unspecified causes
Tuberculous meningitis	
A17	Tuberculosis of nervous system
A17.1	Meningeal tuberculoma (G07*)
A17.8	Other tuberculosis of nervous system
A17.9	Tuberculosis of nervous system, unspecified (G99.8*)
A17.X	Tuberculosis of nervous system

Ethics Approval from University of Cape Town

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

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31 March 2021

HREC REF: 191/2021

Prof M Davies
CIDER
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Dear Prof Davies

PROJECT TITLE: CHARACTERISTICS OF AND RISK FACTORS FOR INFECTIOUS DISEASE HOSPITAL ADMISSIONS IN CHILDREN BY HIV-EXPOSURE STATUS IN AN ERA OF HIGH MATERNAL PREVENTION OF MOTHER TO CHILD HIV TRANSMISSION COVERAGE IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA-DOCTORATE CANDIDATE-MISS SHANI DE BEER-SUB-STUDY LINKED TO 541/2015

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

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 April 2022.

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/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Miss Shani de Beer will also be involved in this study.

Please quote the HREC REF 191/2021 in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) 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.

Chapter 3 appendix

Women with a HIV test vs. women with an unknown HIV status among children classified HUU with low certainty

Appendix Table 3.1: Children classified HUU with low certainty divided into those whose mothers had ≥1 negative HIV test result and those whose mothers had an unknown HIV status, by year of birth

Birth year	2008 – 2011	2012 – 2015	2016 – 2018	Total
		At 1 year of age		
CHILDREN HUU LOW CERTAINTY – N	90,639	160,836	178,716	430,191
Women with ≥1 negative HIV test – N (%)	2,372 (2.6)	9,020 (5.6)	12,247 (6.7)	23,639 (5.5)
Women with an unknown HIV status (i.e. no HIV test) – N (%)	88,267 (97.4)	151,816 (94.4)	166,469 (93.2)	406,552 (94.5)
		At 3 years of age		
CHILDREN HUU LOW CERTAINTY – N	91,427	163,249	181,536	436,212
Women with ≥1 negative HIV test – N (%)	3,259 (3.6)	11,555 (7.1)	15,203 (8.4)	30,017 (6.9)
Women with an unknown HIV status (i.e. no HIV test) – N (%)	88,168 (96.4)	151,694 (92.9)	166,333 (91.6)	406,195 (93.1)
		At first infectious disease hospitalisation		
CHILDREN HUU LOW CERTAINTY – N	4,096	13,789	21,879	39,764
Women with ≥1 negative HIV test – N (%)	151 (3.7)	922 (6.7)	1,648 (7.5)	2,721 (6.8)
Women with an unknown HIV status (i.e. no HIV test) – N (%)	3,945 (96.3)	12,867 (93.3)	20,231 (92.5)	37,043 (93.2)

Abbreviations – HUU: HIV unexposed uninfected

Chapter 4 appendix

Publication from Chapter 4

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RESEARCH ARTICLE

Change in HIV-related characteristics of children hospitalised with infectious diseases in Western Cape, South Africa, 2008–2021: a time trend analysis

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Abstract

Introduction: With the scaling up of vertical HIV transmission prevention programmes, the HIV-related population profile of children in South Africa has shifted. We described temporal changes in HIV-related characteristics of children, aged ≤3 years (up to the third birthday), with infectious disease hospitalisations across the Western Cape province.

Methods: We used routinely collected electronic data to identify children born in the Western Cape with infectious disease hospital records for lower respiratory tract infections, diarrhoea, meningitis and tuberculous meningitis, from 2008 to 2021. Linked maternal and child unique identifiers were used to extract pregnancy, HIV-related, laboratory, pharmacy and hospitalisation data. We described temporal changes in child HIV exposure and acquisition status, timing of maternal HIV diagnosis and antiretroviral therapy (ART) start, infant exposure to maternal ART and timing thereof, and maternal CD4 and HIV viral load closest to delivery. We used logistic and multinomial regression to assess changes in characteristics between the Pre-Option B+ (2008–2013), Option B+ (2013–2016) and Universal ART periods (2016–2021).

Results: Among 52,811 children aged ≤3 years with hospitalisations, the proportion living with HIV dreased from 7.0% (2008) to 1.1% (2021), while those exposed to HIV and uninfected increased from 14.0% (2008) to 16.1% (2021) with a peak of 18.3% in 2017. Among mothers with HIV ($n = 9873$), the proportion diagnosed with HIV and starting ART before pregnancy increased from 20.2% to 69.2% and 5.8% to 59.0%, respectively, between 2008 and 2021. Children hospitalised during the Universal ART period had eight times higher odds (Odds Ratio: 8.41; 95% CI: 7.36–9.61) of exposure to maternal ART versus children admitted Pre-Option B+. Among mothers of children exposed to HIV and uninfected with CD4 records ($n = 7523$), the proportion with CD4 <350 cells/μl decreased from 90.6% (2008) to 27.8% (2021).

Conclusions: In recent years, among children hospitalised with infectious diseases, there were fewer children with perinatally acquired HIV, while an increased proportion of those without HIV acquisition are exposed to maternal HIV and ART. There is a need to look beyond paediatric HIV prevalence and consider child exposure to HIV and ART among children without HIV, when assessing the HIV epidemic's impact on child health services.

Keywords: HIV exposure; HEU; hospitalisation; infectious disease; vertical HIV transmission prevention; South Africa

Additional information may be found under the Supporting Information tab of this article.

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1 | INTRODUCTION

Infectious diseases are a leading cause of paediatric morbidity and mortality and place a burden on public healthcare services, particularly those that are already stretched [1–4]. Evidence suggests that both HIV acquisition and exposure without HIV acquisition are associated with infectious diseases. Between 1992 and 1997, HIV prevalence among paediatric admissions at an urban hospital in South Africa (SA) increased from 2.9% to 20.0%[5, 6], with a related increase in infectious diseases admissions. Furthermore, children exposed to HIV and uninfected (HEU) have been reported to have a higher risk of infection-related morbidity than children unexposed to HIV and uninfected (HUU) [7, 8].

The last two decades have seen substantial scale-up and success of vertical HIV transmission prevention (VTP) in SA

[9]. This success was largely attributable to increased access to antiretroviral therapy (ART) for pregnant people living with HIV, with improved and simplified guideline recommendations. In 2004, ART was only recommended in pregnancy for those with CD4 count <200 cells/μl; in 2008, ART was expanded to those with CD4 <350 cells/μl [9, 10]. Only in 2015 (2013 in the Western Cape province of SA) did ART become available to all pregnant and breastfeeding persons living with HIV, regardless of CD4 count ("Option B+") [11]. In 2016, ART became universally available to all persons living with HIV, meaning more of them would have access to ART before their first pregnancy [12]. Consequently, SA has seen a shift in the HIV-related profile of children under the age 15 years; between 2000 and 2018 HIV prevalence in children decreased by 74.0%, while the proportion who are HEU increased over seven-fold, accounting for 21.6% of all children (age 0–14 years) in SA in 2018 [13, 14]. Furthermore, ART coverage in pregnancy in SA was 96.0% in 2019 [15, 16], meaning that most children HEU are exposed to ART during gestation. Studies have previously used HIV prevalence among hospitalised children as an indicator of the HIV epidemic's impact on child health services [6, 17]. However, with the growing population of children HEU, and evidence that in utero HIV and ART exposure are also associated with child health outcomes in the absence of child HIV acquisition [13], it is also important to measure these characteristics, to more comprehensively understand the effect of the HIV epidemic on child health services.

We aimed to describe, at a provincial-level, the temporal changes in HIV-related characteristics of children hospitalised with infectious diseases from 2008 to 2021, using longitudinal individual-level routine care data from the Western Cape Provincial Health Data Centre.

2 | METHODS

2.1 | Study design and data source

This retrospective, population-based analysis used digitised routine maternal and child healthcare data from the Western Cape Provincial Health Data Centre. The data centre is an electronic health information platform that uses a unique health identifier to consolidate multiple sources of individual-level data from provincial public sector health services in the Western Cape [18]. Data including hospital admissions, outpatient visits, laboratory test results and pharmacy records are linked into a single individual-level data repository. Data on mothers and children are also electronically linked.

2.2 | Study setting

The Western Cape, one of SA's nine provinces, has an estimated population of seven million [18]. The province's antenatal HIV prevalence increased from 16.1% (2008) to 17.9% (2019) [15]. About three-quarters of the population, including most persons living with HIV, utilise public-sector health services [18, 19]. The public sector includes 51 hospitals consisting of District, Regional, Tertiary and Central hospitals [20]. District hospitals are the usual entry point into the hospital system, with complicated cases being referred to Regional, Tertiary or Central hospitals for specialist care [21]. In the late 1990s and early 2000s, ill children, particularly children with HIV (CWH) or children HEU, were admitted to Tertiary/Central hospitals. However, over time, there have been changes to paediatric healthcare organisation in SA, with increased district hospital capacity and less dependence on tertiary hospitals [22, 23].

2.3 | Study participants

We used routinely collected electronic data to identify children born in the Western Cape between 2008 and 2018, with a known live birth outcome, who had infectious disease hospitalisation records for lower respiratory tract infection (LRTI) (including influenza, viral, bacterial and congenital pneumonias, and bronchitis), diarrhoea, meningitis or tuberculous meningitis (TBM), from 2008 to 2021 (Supplementary Figure 1). We included first admissions in children hospitalised aged ≤3 years (by their third birthday). Within the Western Cape Provincial Health Data Centre, hospital admissions are classified using ICD-10 codes. Admissions with more than one of the above infectious diagnoses were counted in each relevant category.

To accurately classify child HIV acquisition and in utero HIV exposure, children were excluded if they could not be linked to their mothers, if child HIV-positive status was confirmed after hospital discharge but with unknown timing of acquisition, if their mothers were diagnosed with HIV more than 10 weeks after child's date of birth (10 weeks postnatal was used as a reasonable time-period to consider that maternal HIV acquisition might have occurred during pregnancy) or if they or their mothers had data inconsistencies (e.g. a negative HIV-PCR result after evidence of having HIV).

2.4 | Procedures and measurements

We extracted data on demographics, pregnancy, HIV testing, HIV evidence, ART start and dispensary dates, laboratory test results (HIV PCR and ELISA, CD4 count and viral load) and death from the Western Cape Provincial Health Data Centre. Using HIV-related data, including data on most recent negative HIV test results relative to the time of hospital admission, we categorised the in utero HIV exposure status and HIV acquisition status of each child at infectious disease hospitalisation discharge date as CWH, HEU or HUU, according to simplified DECIPHER (Data Evaluation and Collaborative Initiation for Paediatric HIV Education and Research) definitions (Table S1) [24]. Children who tested positive were considered HIV negative until their last negative HIV test and to have an unknown HIV status thereafter until the date of first HIV evidence. CWH whose mothers were not known to be living with HIV were included for assessing change in HIV acquisition status over time, but excluded for the analysis of other HIV-related characteristics.

For mothers with HIV, we categorised timing of maternal HIV diagnosis (before pregnancy, during pregnancy, at delivery/postnatally); timing of maternal ART start (before pregnancy, during pregnancy, delivery/postnatally, no ART evidence); infant exposure to maternal ART (yes/no) by using ART dispensing dates to determine if mothers were on ART

at any point between conception and 3 months post-delivery; timing of earliest infant exposure to maternal ART (at conception, early/middle gestation [post-conception to 3 months pre-delivery], late gestation/postnatally [within 3 months pre or post-delivery]) based on the earliest point mothers were dispensed ART between conception and 3 months post-delivery; maternal CD4 count (<350 cells/μl, 350–499 cells/μl, ≥500 cells/μl) and viral load (<1000 copies/ml, ≥1000 copies/ml), using records closest to delivery, within a 365-day window of delivery. We described these characteristics over time by year of infectious disease hospital admission. We categorised the time of hospital admission into periods: January 2008–April 2013 (Pre-Option B+), May 2013–August 2016 (Option B+) and September 2016–December 2021 (Universal ART).

2.5 | Statistical analyses

We described and assessed differences in non-HIV-related child and maternal characteristics, by categorised year of admission, using proportions (categorical variables) and means or medians (continuous variables). We plotted trends in the proportions of different HIV-specific characteristics among hospitalised children. Statistical evidence for changes in proportions across the three time periods was assessed using univariable logistic and multinomial regression models, for binary and non-binary categorical variables, respectively, with the HIV-related characteristic as the dependent variable and time (in periods) as the independent variable. All statistical analyses were done using STATA 17.0 [25, 26].

2.6 | Ethics

This analysis was approved by the University of Cape Town Human Research Ethics Committee (REF 101/2021).

A waiver of informed consent was obtained for this research as all data had already been routinely collected by health services and no participant recruitment was required.

3 | RESULTS

Between 2008 and 2018, there were 54,181 children (born at Western Cape public health facilities) who had a hospital admission record for at least one of the four infectious diseases of interest by age 3 years, of whom 52,811 (97.5%) were included in our analysis (Figure S1). Of the 1370 children who were excluded from our analysis, 70% had mothers diagnosed with HIV postnatally. The main difference between them and children included in the analysis was the proportion of child deaths by age 3 (2.4% vs. 1.5%) and the proportion of maternal deaths by child age 3 (1.1% vs. 0.5%). Of the admissions, 64.9% included LRTI, 36.5% diarrhoea, 4.0% meningitis and 0.6% TBM. The number of annual admissions varied substantially during the study period, with 75.5% of all admissions occurring from 2015 onwards (Table S2).

3.1 | Non-HIV-related characteristics of infants and mothers

Among children included, 56.4% were male and 1.5% died before the age 3 years (Table 1). The proportion of admitted children with very low (1000–1499 g) and low birthweight (1500–2499 g) decreased between the Pre-Option B+, Option B+ and Universal ART periods from 8.3% to 4.8% to 3.2% and 23.3% to 19.0% to 17.0%, respectively. Mean maternal age at delivery remained constant at 27 years throughout, while the proportion of mothers who died by child age 3 years decreased from 1% Pre-Option B+ to 0.5% during Option B+ and 0.4% during the Universal ART period.

3.2 | HIV-related characteristics of infants and mothers

3.2.1 | *Infant HIV exposure and HIV acquisition status*

By hospital discharge, 17.0% of children were HEU, 81.2% HUU and 1.9% CWH (Table 1). The certainty of the combined HIV exposure and acquisition status of most (56.4%) children HEU was high, but low for most children HUU (92.8%) (Table S3). The proportion of CWH among infectious disease admissions decreased from 7.0% in 2008 to 1.1% in 2021. The proportion of children classified as HEU at hospital discharge increased from 14.1% in 2008 to 16.1% in 2021, with a peak of 18.3% in 2017 (Figure 1.1). Children hospitalised with infectious diseases were less likely to have HIV, compared to being HEU, during the Option B+ (Relative Risk Ratio [RRR]: 0.35; 95% CI: 0.29–0.42) and Universal ART (RRR: 0.26; 95% CI: 0.22–0.31) periods, relative to children admitted during the Pre-Option B+ period (Figure 1.2).

3.2.2 | *Maternal HIV diagnosis and ART start time*

Of CWH, 7.6% of mothers did not have evidence of HIV and were excluded from further analysis (Table S4). A descriptive summary of the proportion of mothers in respective maternal HIV diagnosis and ART start categories is shown in Table S5. Among mothers of hospitalised children HEU and CWH, who were living with HIV, the proportion diagnosed with HIV before pregnancy increased from 20.2% in 2008 to 69.2% in 2021, with a peak of 75.2% in 2020 (Figure 2.1). Mothers were more likely to have been diagnosed with HIV before pregnancy, versus during pregnancy, among children admitted during the Option B+ and Universal ART periods, compared to children admitted before the Option B+ period (Figure 2.2).

The proportion of mothers with HIV (N = 9873) starting ART before pregnancy increased from 5.8% in 2008 to 59.0% in 2021, peaking at 62% in 2020 (Figure 3.1), with mothers more likely to have started ART before pregnancy, versus at delivery/postnatally, among children admitted during the Option B+ and Universal ART periods, compared to children admitted before the Option B+ period (Figure 3.2).

3.3 | Infant exposure to maternal ART

The proportion of children exposed to HIV (HEU and CWH) who were exposed to maternal ART increased from 16.3% in 2008 to 87.2% in 2021 (Figure S2.1). The odds of having been exposed to maternal ART increased eight-fold (Odds Ratio: 8.41; 95% CI: 7.36–9.61) for children admitted to the hospital during the Universal ART period compared to children admitted before the Option B+ period (Figure S2.2).

Table 1. Characteristics of infants (and their mothers), born in Western Cape from 2008 to 2018, who had an infectious disease hospital admission (LRTI, diarrhoea, meningitis and TBM), by different ART policy periods (Pre-Option B+, Option B+ and Universal ART)

	Infectious disease hospitalisation			
Variable	Total N = 52,811 (100%)	Pre-Option B+ (A) n = 7223 (13.7%)	Option B+ (B) n = 16,030 (30.4%)	Universal ART (C) n = 29,558 (56.0%)
Infant Characteristics				
Sex: *n* (%)				
Male	29,761 (56.4)	4052 (56.1)	9101 (56.8)	16,608 (56.2)
Missing	15 (0.03)	0 (0)	4 (0.02)	11 (0.03)
Birthweight (g): *n* (%)				
Foetal macrosomia (≥4000 g)	1799 (3.4)	233 (3.2)	528 (3.3)	1038 (3.5)
Normal (2500–3999 g)	37,830 (71.6)	4448 (61.6)	11,316 (70.6)	22,066 (74.7)
Low (1500–2499 g)	9759 (18.5)	1681 (23.3)	3042 (19.0)	5036 (17.0)
Very low (1000–1499 g)	2318 (4.4)	600 (8.3)	774 (4.8)	944 (3.2)
Extremely low (<1000 g)	926 (1.8)	251 (3.5)	330 (2.1)	345 (1.2)
Missing	179 (0.3)	10 (0.1)	40 (0.3)	129 (0.4)
Mean (95% CI)	2868 (2862; 2874)	2684 (2665; 2704)	2844 (2832; 2856)	2926 (2918; 2934)
Twins: *n* (%)				
	2252 (4.3)	525 (7.3)	716 (4.5)	1011 (3.4)
Died before 3 years of age (all-cause): *n* (%)				
	808 (1.5)	276 (3.8)	242 (1.5)	290 (1.0)
Age (months) at first infectious-cause hospitalisation				
Median (IQR)	7.27 (11.97)	4.73 (8.35)	5.85 (9.86)	9.01 (13.58)
Exposure and HIV acquisition status at time of hospital discharge: *n* (%)				
Children HEU	8969 (17.0)	1025 (14.2)	2802 (17.5)	5142 (17.4)
Children HUU	42,864 (81.2)	5899 (81.7)	12,942 (80.7)	24,023 (81.3)
Children with HIV	978 (1.9)	299 (4.1)	286 (1.8)	393 (1.3)
Maternal Characteristics				
Age (years) at delivery:				
Mean (95% CI)	27.20 (27.11; 27.22)	27.23 (27.09; 27.38)	27.09 (26.99; 27.19)	27.19 (27.12; 27.26)
Missing: *n* (%)	243 (0.5)	48 (0.7)	77 (0.5)	118 (0.4)
Maternal death by child age 3 years: *n* (%)				
	253 (0.5)	74 (1.0)	73 (0.5)	106 (0.4)

Note: Pre-Option B+ (January 2008–April 2013); Option B+ (May 2013–August 2016); Universal ART (September 2016–December 2021).
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HEU, exposed to HIV and uninfected; HUU, unexposed to HIV and uninfected; IQR, interquartile range; LRTI, lower respiratory tract infection; TBM, tuberculous meningitis.

Among children exposed to maternal ART, the proportion exposed for the first time during late gestation/postnatally decreased from 58.8% in 2008 to 17.6% in 2021 (Figure S3.1). Children admitted to hospital with an infectious disease during the Option B+ and Universal ART periods were more likely to have first been exposed to maternal ART at conception, relative to late gestation/postnatally, compared with children admitted before the Option B+ period) (Figure S3.2).

3.4 | Maternal viral load and CD4 count closest to pregnancy start

Among hospitalised children HEU with mothers who had viral load tests, >80% of mothers had viral loads <1000 copies/ml for all years except 2010 (72.7%) (Figure 4.1). Mothers of children HEU were more likely to have viral loads <1000 copies/ml (vs. ≥1000 copies/ml) for children admitted during the Universal ART period, compared to the period Pre-Option B+ (Figure 4.3). Among hospitalised CWH, the proportion of mothers with viral loads <1000 copies/ml peaked at 58.3% in 2009 and decreased to 25% in 2021 (Figure 4.2). Mothers of hospitalised CWH were less likely to have viral loads <1000 copies/ml (vs. ≥1000 copies/ml), for children admitted during the Option B+ period, compared to children admitted before the Option B+ period (Figure 4.4).

Among hospitalised children HEU with mothers who had a CD4 count recorded, the proportion of mothers with CD4 count <350 cells/μl decreased from 90.6% in 2008 to 27.8% in 2021 (Figure 5.1). Among hospitalised CWH, the proportion of mothers with a CD4 count <350 cells/μl was 70.8% in 2008 and 75.0% in 2021, with a minimum of 41.2% in 2020 (Figure 5.2). Mothers of hospitalised children HEU were more

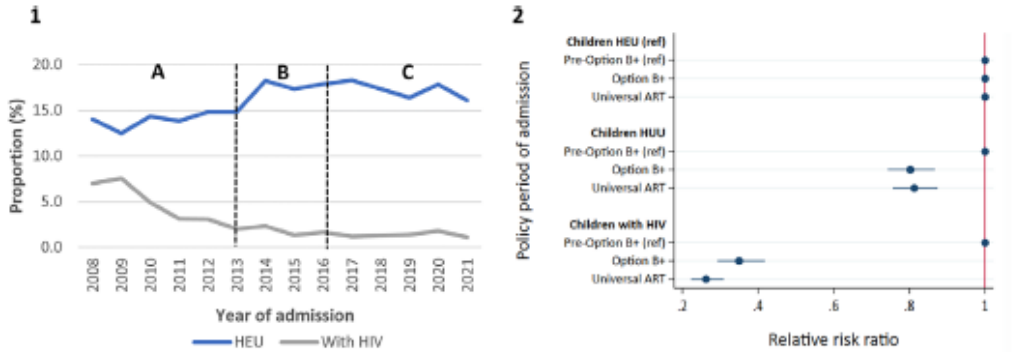

Figure 1. HIV exposure and aquisition status. [1]—Trends in HIV exposure and aquisition status among children HEU and CWH who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [2]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regressions assessing the association between child HIV exposure and aquisition status with policy period of hospital admission. *N* = 52,811. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; HUU, unexposed to HIV and uninfected; ref, reference group.

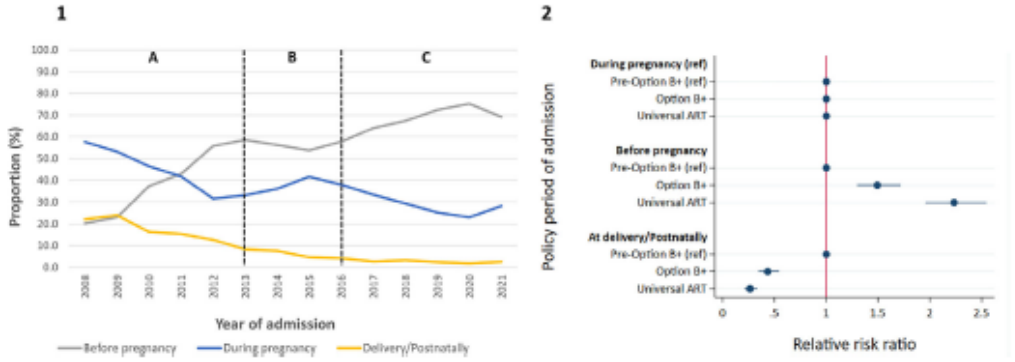

Figure 2. Timing of HIV diagnosis. [1]—Trends in timing of HIV diagnoses among mothers of children HEU and CWH, who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [2]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of mother HIV diagnosis (relative to pregnancy and delivery) with policy period of hospital admission. *N* = 9,873. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

likely to have a CD4 count ≥500 cells/μl (vs. <350 cells/μl), for children admitted during the Option B+ (RRR: 3.54; 95 CI%: 2.90–4.31) and Universal ART periods (RRR: 4.74; 95 CI%: 3.92–5.73), compared to children admitted before the Option B+ period (Figure 5.3). Mothers of hospitalised CWH were less likely to have a CD4 count ≥500 cells/μl (vs. <350 cells/μl), for children admitted during the Universal ART period (RRR: 0.61; 95 CI%: 0.40–0.93), compared to children admitted before the Option B+ period (Figure 5.4).

4 | DISCUSSION

Since the scale-up of VTP in SA from 2002, tremendous gains have been made in preventing and treating paediatric HIV acquisition [9, 27]. Our findings demonstrate how the HIV-related profile of children hospitalised for infectious diseases has changed from 2008 to 2021 in the Western Cape, in the context of guideline amendments.

During the scale-up of VTP, the stabilisation of antenatal HIV prevalence and reduction in vertical HIV transmission resulted in a progressive decline in the CWH population and consequent increase in the prevalence of children HEU, since 2004 [27]. Thembisa model estimates show a decrease in HIV prevalence, among children under the age 3 years in the Western Cape, from 1.0% in 2008 to 0.4% in 2021 [28]. While we do not have estimates for the prevalence of children HEU in the Western Cape, UNAIDS estimates of the national prevalence of children HEU (0–14 years) in SA increased from 11.8% in 2008 to 21.6% in 2018 [13]. Antenatal HIV prevalence in SA is higher than in the Western Cape (30.0% vs. 18.9% in 2019), therefore, we expect the prevalence of

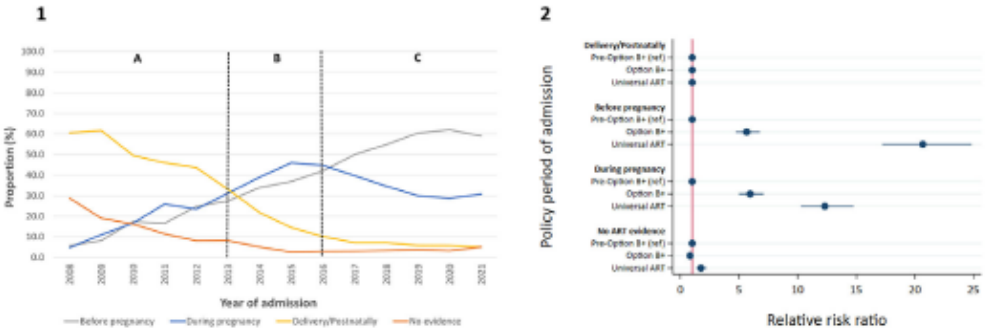

Figure 3. Timing of ART start. [1]—Trends in timing of ART start among mothers of children HEU and CWH who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [2]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of mother's ART start (relative to pregnancy and delivery) with policy period of hospital admission. *N* = 9873. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

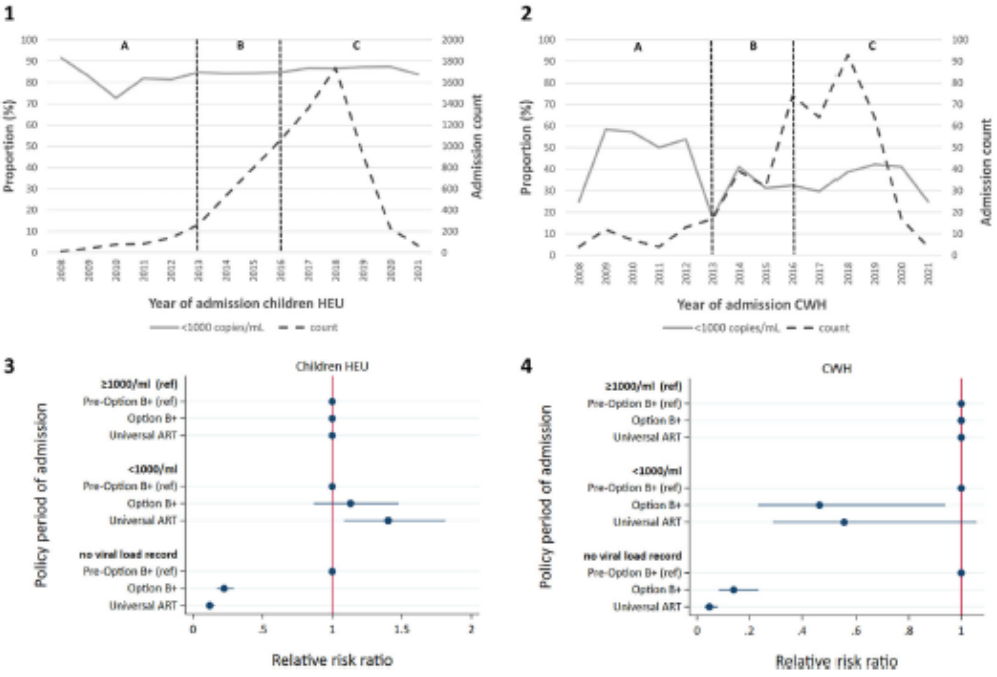

Figure 4. Maternal viral load. [1] and [2]—Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis) hospital admittees HEU [1] (*n* = 7306) or with HIV [2] (*n* = 444) whose mothers had a viral load of <1000 copies/ml during pregnancy (including only mothers with a viral load record). The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [3] and [4]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of maternal viral load during pregnancy with policy period of hospital admission, for children HEU [3] (*N* = 8969) and CWH [4] (904), respectively. *We had no viral load record for 1663 (18.5%) of mothers to children HEU and 460 (51.0%) of CWH. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

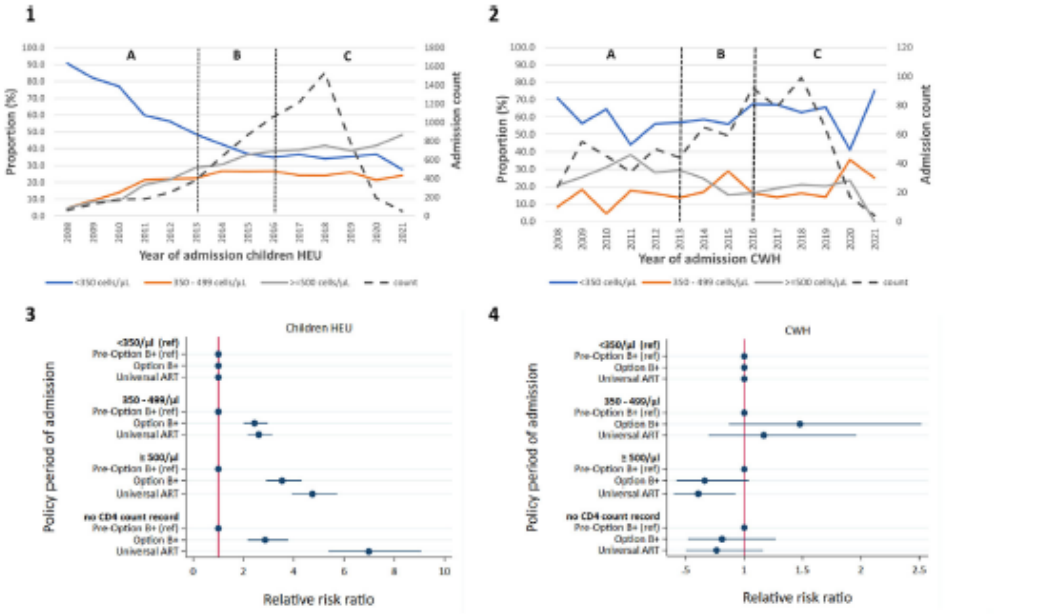

Figure 5. Maternal CD4 count. [1] and [2]—Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis) hospital admittees HEU [1] (*n* = 7523) or with HIV [2] (*n* = 731) whose mothers had CD4 count <350 cells/µl, 350–499 cells/µl or ≥500 cells/µl during pregnancy (including only mothers with a CD4 count record). The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [3] and [4]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of mother CD4 count during pregnancy with policy period of hospital admission, for children HEU [3] (*n* = 8969) and CWH [4] (*n* = 904), respectively. *We had no CD4 count record for 1456 (16.2%) of mothers to children HEU and 173 (19.1%) of CWH. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

children HEU to be correspondingly lower in the Western Cape and that the average prevalence of children HEU between 2008 and 2018 (the birth cohorts of this analysis) would be lower than 17% [15]. These patterns are reflected in our analysis. During the 14-year period under analysis, the proportion of CWH among infectious disease hospital admittees age ≤3 years dropped from 7.0% in 2008 to 1.3% in 2018. This corresponded with an increase in the proportion of children HEU from 14.1% in 2008 to 17.3% in 2018. With an average prevalence of children HEU over the study period of 17%, this suggests an over-representation of hospitalised children HEU than in the general population. A study by Meyers et al. also showed a decreasing trend in the HIV prevalence among hospital admittees (0–14 years), although the HIV prevalence among hospital admittees that they reported for 2007 and 2010/11 (29.5% and 19.3%) was substantially higher than what we observed in 2008 and 2010, respectively [17]. The Meyers et al. study was conducted at a single large urban academic hospital in Gauteng province, which has a higher HIV prevalence among children than Western Cape, and results may not be generalizable to our province-wide setting in the Western Cape.

The introduction of Option B+ has improved access to ART for all pregnant people living with HIV and dramatically reduced vertical HIV transmission [9]. In the Western Cape, between 2010 and 2013, Myer et al. observed a substantial increase in the proportion of pregnant people living with HIV entering antenatal care on ART, and initiating ART before delivery [29]. They also reported a substantial reduction in delays to antenatal ART initiation after CD4 eligibility criteria were removed during the Option B+ period. In our analysis, mothers of children admitted to hospital in the Option B+ and universal ART periods, compared to Pre-Option B+, were significantly more likely to have been diagnosed with HIV before pregnancy versus during pregnancy and to have initiated ART before or during pregnancy versus at delivery/postnatally. As a result, the proportion of children exposed to maternal ART increased over time, with children admitted during universal ART versus Pre-Option B+, having eight times higher odds of maternal ART exposure. Furthermore, with mothers initiating ART earlier, children admitted in the later periods, compared to Pre-Option B+, were more likely to have been exposed to maternal ART for the first time at conception versus late gestation/postnatally. The apparent slight increase from 2016 onwards in the proportion who had no ART evidence among mothers with HIV may be due to better ascertainment of maternal HIV status in this period.

Throughout the study period, mothers of CWH at the time of infectious disease hospital admission predominantly had viral loads ≥1000 copies/ml near delivery, while the

proportion of mothers of children HEU with viral loads <1000 copies/ml near delivery was >80% for all years except 2010. This is expected, given that the risk of vertical HIV transmission is increased with a higher maternal viral load, particularly ≥1000 copies/ml [30, 31].

As access to maternal ART improved over the years, and CD4 count was no longer recommended for monitoring persons living with HIV who are virally suppressed on ART, the proportion of mothers of children HEU who had CD4 count recorded reduced, as did the proportion with CD4 <350 cells/μl near delivery, suggesting that maternal ART has not only reduced vertical HIV transmission, but also improved maternal health, as expected. The reduction in maternal deaths by the time of child age 3 years supports this. We found that among CWH admittees, mothers predominantly had CD4 counts <350 cells/μl near delivery, corresponding with high viral loads observed in these mothers, suggesting that mothers not optimally sustaining ART in the context of a high coverage effective VTP programme remain especially vulnerable.

4.1 | Strengths and limitations

The Western Cape Provincial Health Data Centre provided a novel opportunity to assess, province-wide, the real-world trends in HIV-related characteristics of hospitalised children, using individual-level longitudinal health service data. We were also able to classify HIV exposure and acquisition status of children at the time of hospitalisation, according to standardised certainty definitions [32], enabling better comparability with other studies that use the same definitions.

A limitation is that not all children were classified by HIV exposure and acquisition status with high certainty, particularly children HUU, of whom >90% were classified with low certainty (largely because Rapid point-of-care HIV results are not routinely digitised). It is possible that CWH may have been misclassified as HEU and children HEU as HUU. However, due to high rates of antenatal HIV testing within SA (>95%) [9], we are confident that most mothers living with HIV would have been identified during pregnancy, thereby limiting the misclassification of children exposed to HIV as unexposed. Additionally, of the children excluded from our analysis (n = 1370), 70% had mothers diagnosed with HIV postnatally. We may, therefore, have a slight underestimation of children HEU or with HIV in our sample.

Another limitation of our findings is the accuracy and completeness of ICD-10 codes, particularly in the earlier years of the analysis. Our classification of hospital admissions due to infectious causes relied on ICD-10 codes, which were previously shown to have poor reliability [33]. However, in more recent years, the implementation of a standardised discharge summary has improved ICD-10 code completeness and accuracy [34], likely resulting in improved identification of infectious cause hospitalisations. As a result, a large proportion of admissions included in our analyses were from 2015 onwards. Furthermore, it is probable that in the earlier years, admission codes were captured more accurately in tertiary hospitals and among more severely sick children. In the Pre-Option B+ period, >70% of admissions in our analyses were to tertiary hospitals (not shown), whereas >70% were to non-tertiary hospitals during the universal ART period. It is possible that the Pre-Option B+ cohort is more representative of severely ill children than the cohorts of children admitted in the later periods, potentially overestimating the prevalence of CWH, and other risk factors for severe disease, particularly low birth weight.

We did not include children born out of the province who relocated to and were hospitalised in the Western Cape. We also only considered four infectious diseases that cause substantial morbidity and mortality in children. Other childhood infections, including pulmonary tuberculosis, were not included in this analysis. Our results may, therefore, not be generalizable to all child infectious diseases burdening the healthcare system.

5 | CONCLUSIONS

Temporal trends among children hospitalised with infectious diseases highlight the positive impact of VTP and increased ART access within SA. Whereas children of mothers with HIV were previously exposed to no or short-duration maternal ART, in recent years, the majority were exposed to maternal ART, frequently from early gestation. There were fewer CWH and a higher proportion of children HEU in recent years.

However, the finding that at least one in six children hospitalised in recent years were HEU, of which up to 87% were exposed to maternal ART, highlights the need to consider HIV and ART exposure status, and not just child HIV prevalence, when assessing the impact of the HIV epidemic on child health services. Further research is needed to quantify the burden of infectious diseases on the health system that is due to higher risk among children HEU relative to children HUU and whether there is a need for HEU-specific interventions in addition to interventions that improve the health and wellbeing of all children in resource-limited settings.

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COMPETING INTERESTS

KA, EK, AB and M-AD receive funding from ViiV Healthcare for an unrelated project.

AUTHORS' CONTRIBUTIONS

STdB, M-AD, ALS, BE, SMI and HEJ conceptualised the research study. STdB managed the data with assistance from FP and insight from M-AD, ALS, KA and EK. AB provided data engineering oversight within the Western Cape Provincial Health Data Centre. STdB conducted the data analyses and drafted the manuscript with subject matter expertise and/or scientific oversight from M-AD, ALS, BE, SMI, HEJ and KA. All authors reviewed and approved the final manuscript.

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Kathleen Kehoe and Erna Modern contributed to the curation and management of the data.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Western Cape Provincial Health Data Centre, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available, however, from the corresponding author upon reasonable request and with permission of the Western Cape Provincial Health Data Centre.

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Figure S1: Flow diagram of mother-infant pairs included in the cohort of children, born in the Western Cape (2008 – 2018), who had an infectious disease hospital admission (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis) by age three years.

Figure S2: Infant exposure to maternal ART. (1) - Trend in the proportion of hospital admittees HEU or with HIV who were exposed to maternal ART and hospitalised with at least

one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A Pre-Option B+, B - Option B+, C - Universal ART; **(2)** - Plot of the odds ratios (with 95% confidence intervals) from logistic regression assessing the association of infant exposure to maternal ART with policy period of hospital admission. N = 9,873.

Figure S3: Timing of earliest infant exposure to maternal ART. (1) - Trends in the proportion of hospital admittees' earliest exposure to maternal ART at different time points, among those who were exposed to maternal ART and hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A Pre-Option B+, B - Option B+, C - Universal ART; **(2)** - Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of initial infant exposure to mother's ART start (relative to pregnancy and delivery) with policy period of hospital admission. N = 7,612.

Table S1: Simplified DECIPHER definitions for classification of children as HEU and HUU from routinely-collected data.

Table S2: Count and proportion of hospital admissions per year

Table S3: Certainty of HIV exposure status in children born to women with and without HIV, in Western Cape, South Africa (2008-2021), at hospitalisation.

Table S4: Number of mothers and children with evidence for maternal HIV, maternal ART, Infant exposure to maternal ART, maternal viral loads and maternal CD4 counts, among children HEU and with HIV.

Table S5: Descriptive statistics for Maternal HIV diagnosis and Maternal ART start across the three policy periods, for mothers who had evidence of an HIV diagnosis (N=9,873).

Characteristics of included and excluded children

Appendix Table 4.1: Characteristics of children (and their mothers), born in Western Cape from 2008 – 2018, who had an infectious disease hospital admission (LRTI, diarrhoea, meningitis, TBM), by those included and excluded in Chapter 4 analyses

Variable	Total N=54,177 (100%)	Children included N=52,811 (97.5%)	Children excluded N=1,366 (2.5%)
CHILD CHARACTERISTICS			
Sex: n (%)			
Male	30,519 (56.3)	29,761 (56.4)	758 (55.5)
Missing	10 (0.02)	9 (0.02)	1 (0.07)
Birth weight (g): n (%)			
Fetal macrosomia (≥4000g)	1,845 (3.4)	1,799 (3.4)	46 (3.4)
Normal (2500g – 3999g)	38,756 (71.5)	37,830 (71.6)	926 (67.8)
Low (1500g – 2499g)	10,054 (18.6)	9,759 (18.5)	295 (19.0)
Very Low (1000g – 1499g)	2,387 (4.4)	2,318 (4.4)	69 (5.1)
Extremely Low (<1000g)	950 (1.8)	926 (1.8)	24 (1.8)
Missing	185 (0.3)	179 (0.3)	6 (0.4)
Multiple pregnancy: n (%)	2,324 (4.3)	2,252 (4.3)	72 (5.3)
Missing	22 (0.04)	100 (7.3)	122 (0.2)
Died before 3 years of age (all-cause): n (%)	844 (1.6)	808 (1.5)	36 (2.6)
Age (months) at first infectious-cause hospitalisation			
≤6 days	1,411(2.6)	1,354 (2.6)	57 (4.4)
7days – 27 days	2,491 (4.6)	2,418 (4.6)	73 (5.6)
28 days – 12 months	32,559 (60.5)	31,746 (60.4)	813 (62.8)
>12 – 24 months	12,431 (23.1)	12,171 (23.2)	260 (20.1)
>24 – 36 months	4,960 (9.2)	4,869 (9.3)	91 (7.03)
Children with HIV at time of hospitalisation¥: n(%)	1,057 (2.0)	978 (1.9)	79 (5.8)
MATERNAL CHARACTERISTICS			
Age (years) at delivery:			
Mean (SD)	27.1 (6.3)	27.2 (6.3)	26.1 (6.0)
Missing: n (%)	346 (0.6)	243 (0.5)	103 (7.5)
Maternal death by child age 3 years: n (%)	268 (0.5)	253 (0.5)	15 (1.1)

¥ This proportion includes children who had data inconsistencies

Abbreviations – SD: standard deviation

HIV exposure certainty

Appendix Table 4.2: Certainty of HIV exposure status in children born to women with and without HIV, in Western Cape, South Africa (2008-2021), at hospitalisation

	Prior to Option B+	During Option B+	Universal ART	Total
CHILDREN HEU (N =8,969)				
High certainty N (%)	591 (57.6)	1,765 (63.0)	2,698 (52.5)	5,054 (56.4)
Moderate certainty N (%)	218 (21.3)	738 (26.3)	2,037 (39.6)	2,993 (33.4)
Low certainty N (%)	88 (8.6)	181 (6.5)	308 (6.0)	577 (6.4)
No certainty N (%)	128 (12.5)	118 (4.2)	99 (1.9)	345 (3.9)
CHILDREN HUU (N = 42,864)				
High certainty N (%)	324 (5.5)	472 (3.7)	492 (2.1)	1,288 (3.0)
Moderate certainty N (%)	398 (6.8)	632 (4.9)	782 (3.3)	1,812 (4.2)
Low certainty N (%)	5,177 (87.8)	11,838 (91.5)	22,749 (94.7)	39,764 (92.8)

Abbreviations - ART: Antiretroviral therapy; HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected

Numbers of mothers and children with HIV related evidence

Appendix Table 4.3: Number of mothers and children with evidence for maternal HIV, maternal ART, Infant exposure to maternal ART, maternal viral loads and maternal CD4 counts, among children HEU and with HIV

HIV-related characteristic	Total	Children HEU	Children with HIV
Maternal HIV	**N=9,947**	**N=8,969**	**N=978**
Yes	9,873 (99.3)	8,969 (100.0)	904 (92.4)
No evidence	74 (0.7)	–	74 (7.6)
Maternal ART – N (%)	**N= 9,873**	**N= 8,969**	**N=904**
Yes	9,391 (95.1)	8,576 (95.6)	815 (90.2)
No evidence	482 (4.9)	393 (4.4)	89 (9.9)
Infant exposure to maternal ART – N (%)	**N= 9,873**	**N= 8,969**	**N=904**
Yes	7,612 (77.1)	7,186 (80.1)	426 (47.1)
No evidence	2,261(22.9)	1,783 (19.9)	478 (52.9)
Maternal viral load record – N (%)	**N= 9,873**	**N= 8,969**	**N=904**
Yes	7,750 (78.5)	7,306 (81.5)	444 (49.1)
No	2,123 (21.5)	1,663 (18.5)	460 (51.0)
Maternal CD4 count record – N (%)	**N= 9,873**	**N= 8,969**	**N=904**
Yes	8,244 (83.5)	7,513 (83.8)	731 (80.9)
No	1,629 (16.5)	1,456 (16.2)	173 (19.1)

Abbreviations - ART: Antiretroviral therapy; HEU: exposed to HIV and uninfected

Chapter 5 appendix

Characteristics of included and excluded children

Appendix Table 5.1: Characteristics of children (and their mothers), born in Western Cape from 2013 – 2018, by those included and excluded in Chapter 5 analyses

Variable	Total N=407,342 (100%)	Children included N=398,334 (97.8%)	Children excluded N=9,008 (2.2%)
CHILD CHARACTERISTICS			
Sex: n (%)			
Male	206,033 (50.6)	201,533 (50.6)	4,500 (50.0)
Missing	807 (0.2)	784 (0.2)	23 (0.3)
Birth weight (g): n (%)			
Fetal macrosomia (≥4000g)	16,817(4.1)	16,545(4.2)	272 (3.0)
Normal (2500g – 3999g)	322,348 (79.1)	315,714 (79.3)	6,634 (73.7)
Low (1500g – 2499g)	55,421(13.6)	53,848 (13.5)	1,573 (17.5)
Very Low (1000g – 1499g)	7,606 (1.9)	7,347 (1.8)	259 (2.9)
Extremely Low (<1000g)	3,821 (0.9)	3,600 (0.9)	221 (2.5)
Missing	1,329 (0.3)	1,280 (0.3)	49 (0.5)
Multiple pregnancy: n (%)	11,290 (2.8)	11,045 (2.8)	245 (2.7)
Missing	909 (0.2)	144 (0.04)	765 (8.5)
Died before 3 years of age (all-cause): n (%)	4,932 (1.2)	4,547 (1.1)	385 (4.3)
Birth year: n (%)			
2013 & 2014	104,762 (25.7)	101,552 (25.4)	3,210 (35.6)
2015 & 2016	138,593 (34.0)	135,710 (37.1)	2,883 (32.0)
2017 & 2018	163,987(40.3)	161,072(40.4)	2,915 (32.4)
Area of residence: n (%)			
Metropolitan	276,005 (67.8)	269,648 (67.7)	6,357 (70.6)
Non-metropolitan	125,008 (30.7)	122,489 (30.8)	2,519 (28.0)
Missing	6,329 (1.6)	6,197 (1.6)	132 (1.5)
MATERNAL CHARACTERISTICS			
Age (years) at delivery:			
Mean (SD)	27.4 (6.2)	27.4 (6.2)	26.4 (6.0)
Missing: n (%)	2,186 (0.5)	1,381 (0.4)	805 (8.9)
Parity[¥]: n (%)			
0	252,267 (61.9)	247,008 (62.0)	5,259 (58.4)
1	108,157 (26.6)	106,047 (26.6)	2,110 (23.4)
2	34,426 (8.5)	33,792 (8.5)	634 (7.0)
≥3	11,666 (2.9)	11,426 (2.9)	240 (2.7)
Missing	826 (0.2)	61 (0.02)	765 (8.5)
Maternal death by child age 3 years: n (%)	1,305 (0.3)	1,207 (0.3)	98 (1.1)

[¥]Parity is recorded during current pregnancy and is based on digital evidence of prior pregnancies in the Western Cape only. True parity may therefore be underestimated

HIV exposure certainty

Appendix Table 5.2: Certainty of HIV exposure status in children born to women with and without HIV, in Western Cape, South Africa (2013-2018), at end of follow-up

High certainty N (%)	Moderate certainty N (%)	Low certainty N (%)	No certainty N (%)
CHILDREN HEU (N = 67,978)[¥]			
709 (1.0)	46,792 (68.8)	9,413 (13.8)	11,064 (16.3)
CHILDREN HUU (N = 329,820)[¥]			
1,159 (0.4)	317,394 (96,2)	11,267 (3.4)	–

[¥]N excludes children who had evidence of HIV during the study period subsequent to being classified HEU (n=477) or HUU (n=59) at the start of follow up

Abbreviations – HEU: HIV exposed uninfected; HUU: HIV unexposed uninfected

Models assessing the association between HIV/ART exposure and infectious-cause hospitalisation

Appendix Table 5.3: Poisson regression models assessing the association between HIV/ART exposure and infectious-cause hospitalisation in HIV uninfected children within different age groups. (A) Models were adjusted for maternal age at delivery and suburb of residence; (B) Models were adjusted for maternal age at delivery, suburb of residence and child birth weight

Age group	**Neonatal (days 0 – 27)**		**Post neonatal (28 days – 12 months)**		**(>12 months – 36 months)**	
	A aIRR (95%CI) (N=390,779)	**B aIRR (95%CI) (N=389,540)¥**	**A aIRR (95%CI) (N=387,722)**	**B aIRR (95%CI) (N=386,519)**	**A aIRR (95%CI) (N=386,314)**	**B aIRR (95%CI) (N=385,120)**
HIV/ART exposure						
HUU	Ref	Ref	Ref	Ref	Ref	Ref
HEU – ART before pregnancy and start before Universal ART(<2016)	1.40 (1.21-1.63)	1.39 (1.19-1.62)	1.30 (1.22-1.38)	1.29 (1.22-1.37)	1.10 (1.02-1.19)	1.10 (1.02-1.20)
HEU – ART before pregnancy and start during Universal ART (≥2016)	1.35 (0.90-2.02)	1.37 (0.91-2.04)	1.23 (1.05-1.44)	1.25 (1.07-1.46)	0.91 (0.73-1.14)	0.92 (0.74-1.15)
HEU – ART restart during pregnancy	1.54 (1.21-1.98)	1.52 (1.19-1.94)	1.45 (1.32-1.60)	1.38 (1.26-1.52)	1.09 (0.96-1.25)	1.07 (0.94-1.22)
HEU – ART start during pregnancy	1.44 (1.27-1.63)	1.43 (1.26-1.62)	1.13 (1.08-1.19)	1.11 (1.05-1.17)	0.91 (0.85-0.97)	0.90 (0.84-0.96)
HEU – no ART during pregnancy†	1.49 (1.17-1.90)	1.40 (1.10-1.79)	1.44 (1.31-1.58)	1.30 (1.19-1.44)	1.11 (0.98-1.26)	1.06 (0.93-1.20)
HEU – unknown ART‡	1.31 (0.93-1.85)	1.32 (0.93-1.86)	1.29 (1.14-1.47)	1.29 (1.14-1.47)	1.00 (0.84-1.18)	1.00 (0.84-1.19)
HEU – no ART evidence ever	1.41 (0.97-2.07)	1.37 (0.93-2.02)	0.96 (0.81-1.13)	0.96 (0.81-1.13)	0.85 (0.69-1.05)	0.85 (0.70-1.06)
Maternal age at delivery (years)						
15 – 19	Ref	Ref	Ref	Ref	Ref	Ref
20 – 39	0.89 (0.80-0.99)	0.88 (0.79-0.98)	0.89 (0.85-0.92)	0.88 (0.85-0.92)	0.91 (0.86-0.95)	0.90 (0.86-0.95)
40 – 50	0.76 (0.59-0.97)	0.73 (0.57-0.93)	0.89 (0.82-0.97)	0.84 (0.77-0.91)	0.93 (0.84-1.03)	0.90 (0.81-1.00)
Birth weight (g)	–					
Normal (2500 – <4000)	–	Ref		Ref		Ref
Fœtal Macrosomia (≥4000)	–	1.24 (1.04-1.47)		0.85 (0.79-0.91)		0.97 (0.89-1.06)
Low (1500 – <2500)	–	1.40 (1.27-1.54)		1.63 (1.58-1.69)		1.33 (1.27-1.39)
Very low (1000 – <1500)	–	2.49 (2.07-2.99)		3.76 (3.51-4.02)		2.07 (1.88-2.29)
Extremely low (<1000)	–	3.04 (2.30-4.01)		4.89 (4.38-5.45)		3.18 (2.73-3.70)
Variance of random effect (95% CI): Suburb	0.06 (0.03-0.10)	0.06 (0.03-0.10)	0.16 (0.11-0.22)	0.15 (0.11-0.21)	0.24 (0.17-0.33)	0.24 (0.17-0.32)
Variance of random effect (95% CI): Suburb > Child identifier	–		1.74 (1.58-1.69)	1.63 (1.62-1.73)	2.24 (2.16-2.32)	2.21 (2.14-2.90)

¥As it was not possible to have a repeat admission during the neonatal period, child identifier was not included as a random effect in the neonatal period model
†Maternal ART start date at delivery or postpartum
‡ Maternal ART start before or during pregnancy, but mother not dispensed ART during pregnancy
Abbreviations – ART: Antiretroviral therapy; aIRR: adjusted incidence rate ratio; CI: confidence interval; HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected

Appendix Table 5.4: Unadjusted Poisson regression models assessing factors associated with infectious-cause hospitalisation in children without HIV within different age groups

Age group	**Neonatal (days 0 – 27)**		**Post neonatal (28 days – 12 months)**		**(>12 months – 36 months)**	
	Children HUU uIRR (95%CI)	**Children HEU uIRR (95%CI)**	**Children HUU uIRR (95%CI)**	**Children HEU uIRR (95%CI)**	**Children HUU uIRR (95%CI)**	**Children HEU uIRR (95%CI)**
Maternal age at delivery (years)	0.992 (0.986 – 0.998)	0.996 (0.983-1.01)	0.994 (0.992 – 0.996)	0.999 (0.994-1.00)	0.992 (0.989 – 0.994)	1.00 (0.997-1.01)
15 – 19	Ref	Ref	Ref	Ref	Ref	Ref
20 – 39	0.89 (0.80-1.00)	0.84 (0.57-1.22)	0.86 (0.83-0.90)	0.80 (0.69-0.93)	0.86 (0.82-0.90)	0.83 (0.68-1.03)
40 – 50	0.65 (0.48-0.88)	1.00 (0.6-1.67)	0.83 (0.75-0.91)	0.89 (0.72-1.09)	0.80 (0.71-0.90)	1.14 (0.87-1.51)
Child sex: male	1.21 (1.12-1.32)	1.29 (1.11-1.50)	1.38 (1.34-1.42)	1.41 (1.33-1.50)	1.23 (1.19-1.27)	1.25 (1.15-1.35)
Birth weight (g)						
Normal (2500 - <4000)	Ref	Ref	Ref	Ref	Ref	Ref
Foetal Macrosomia (≥4000)	1.23 (1.02-1.49)	1.25 (0.85-1.84)	0.82 (0.76-0.89)	0.89 (0.75-1.07)	0.93 (0.85-1.02)	0.86 (0.67-1.09)
Low (1500 - <2500)	1.45 (1.30-1.62)	1.21 (0.98-1.48)	1.66 (1.60-1.72)	1.66 (1.54-1.79)	1.39 (1.33-1.46)	1.32 (1.19-1.48)
Very low (1000 - <1500)	2.57 (2.09-3.18)	2.25 (1.57-3.23)	3.84 (3.56-4.14)	3.18 (2.75-3.67)	2.06 (1.85-2.30)	1.89 (1.50-2.38)
Extremely low (<1000)	3.13 (2.30-4.27)	2.49 (1.33-4.65)	4.87 (4.32-5.48)	4.01 (3.09-5.19)	3.11 (2.64-3.66)	2.61 (1.75-3.90)
Multiple pregnancy	1.12 (0.88-1.42)	1.11 (0.76-1.63)	1.90 (1.77-2.05)	1.76 (1.54-2.01)	1.01 (0.90-1.12)	1.26 (1.03-1.54)
Parity						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.05 (0.95-1.16)	1.06 (0.90-1.26)	1.10 (1.06-1.13)	1.08 (1.01-1.15)	1.00 (0.96-1.03)	1.00 (0.92-1.10)
2	1.04 (0.89-1.21)	1.30 (1.03-1.65)	1.21 (1.15-1.28)	1.09 (0.99-1.20)	1.03 (0.97-1.10)	1.01 (0.88-1.16)
≥3	1.28 (1.02-1.59)	1.77 (1.25-2.50)	1.30 (1.20-1.41)	1.37 (1.17-1.60)	0.90 (0.81-1.00)	0.91 (0.71-1.16)
Season of birth						
Summer	Ref	Ref	Ref	Ref	Ref	Ref
Autumn	1.53 (1.37-1.71)	1.38 (1.12-1.69)	1.07 (1.03-1.11)	1.07 (0.99-1.17)	1.01 (0.97-1.06)	0.87 (0.78-0.98)
Winter	1.26 (1.12-1.42)	1.01 (0.81-1.25)	0.83 (0.80-0.87)	0.94 (0.87-1.02)	0.98 (0.93-1.03)	0.90 (0.80-1.01)
Spring	0.94 (0.83-1.07)	0.88 (0.70-1.10)	0.80 (0.77-0.84)	0.87 (0.80-0.95)	0.98 (0.93-1.03)	0.92 (0.82-1.02)
Birth year						
2013	Ref	Ref	Ref	Ref	Ref	Ref
2014	0.83 (0.70-0.99)	1.05 (0.76-1.46)	1.10 (1.03-1.17)	1.00 (0.87-1.14)	1.17 (1.09-1.27)	1.19 (0.98-1.44)
2015	0.96 (0.81-1.23)	0.93 (0.68-1.29)	1.32 (1.24-1.40)	1.16 (1.02-1.31)	1.50 (1.40-1.61)	1.38 (1.16-1.66)
2016	1.02 (0.87-1.13)	0.90 (0.65-1.23)	1.39 (1.31-1.48)	1.19 (1.05-1.35)	1.77 (1.66-1.90)	1.59 (1.33-1.89)
2017	1.15 (0.99-1.35)	1.05 (0.78-1.42)	1.80 (1.70-1.91)	1.41 (1.25-1.59)	1.71 (1.60-1.84)	1.45 (1.22-1.73)
2018	1.53 (1.32-1.77)	1.25 (0.94-1.67)	1.92 (1.82-2.03)	1.37 (1.21-1.54)	1.37 (1.28-1.47)	1.39 (1.17-1.65)

Age group	Neonatal (days 0 – 27)		Post neonatal (28 days – 12 months)		(>12 months – 36 months)	
	Children HUU uIRR (95%CI)	Children HEU uIRR (95%CI)	Children HUU uIRR (95%CI)	Children HEU uIRR (95%CI)	Children HUU uIRR (95%CI)	Children HEU uIRR (95%CI)
CD4 count (pregnancy start):						
≥350 cells/μL	-	Ref	-	Ref	-	Ref
<350 cells/μL	-	0.97 (0.81-1.15)	-	1.10 (1.03-1.18)	-	0.99 (0.90-1.09)
No CD4 record	-	0.96 (0.79-1.16)	-	1.07 (0.99-1.15)	-	1.02 (0.92-1.13)
Viral load (pregnancy start):						
<1000 copies/mL	-	Ref	-	Ref	-	Ref
≥1000 copies/mL	-	1.18 (0.96-1.45)	-	1.27 (1.17-1.37)	-	1.15 (1.03-1.29)
No VL record	-	1.01 (0.82-1.23)	-	1.08 (1.00-1.17)	-	0.97 (0.87-1.08)

Child identifier was included as a random effect in all post neontal and >12 months – 36months period models. As it was not possible to have a repeat admission during the neonatal period, child identifier was not included as a random effect in the neonatal period models.

Abbreviations – CI: confidence interval; HEU: exposed to HIV and uninfected; HUU: unexposed to HIV and uninfected; uIRR: unadjusted incidence rate ratio

Chapter 6 Appendix - Characteristics of included and excluded children

Appendix Table 6.1: Characteristics of children (and their mothers), born in Western Cape from 2013 – 2018, by those included and excluded in Chapter 6 analyses

Variable	Total N=407,342 (100%)	Children included N=390,688 (95.9%)	Children excluded N=16,654 (4.1%)
CHILD CHARACTERISTICS			
Sex: n (%)			
Male	206,033 (50.6)	197,770 (50.6)	8,263(50.0)
Missing	807 (0.2)	777 (0.2)	30 (0.2)
Birth weight (g): n (%)			
Fetal macrosomia (≥4000g)	16,817 (4.1)	16,486 (4.2)	331 (2.0)
Normal (2500g – 3999g)	322,348 (79.1)	312,536 (80.0)	9,812 (58.9)
Low (1500g – 2499g)	55,421(13.6)	50,366 (12.9)	5,055 (30.4)
Very Low (1000g – 1499g)	7,606 (4.4)	6,698 (1.7)	908 (5.5)
Extremely Low (<1000g)	3,821 (1.9)	3,347 (0.9)	474 (2.9)
Missing	1,329 (0.3)	1,255 (0.3)	74 (0.4)
Multiple pregnancy: n (%)	11,290 (2.8)	5,467 (1.4)	5,823 (34.5)
Missing	909 (0.2)	140 (0.04)	769 (4.6)
Died before 2 years of age (all-cause): n (%)	4,591 (1.1)	4,238 (1.1)	353 (2.1)
Birth year: n (%)			
2013 & 2014	104,762 (25.7)	99,326 (25.4)	5,436 (32.6)
2015 & 2016	138,593 (34.0)	133,081 (34.1)	5,512 (33.1)
2017 & 2018	163,987(40.3)	158,281 (40.5)	5,706 (34.3)
Area of residence: n (%)			
Metropolitan	276,005 (67.8)	263,723 (67.5)	12,282 (73.8)
Non-metropolitan	125,008 (30.7)	120,882 (30.9)	4,126 (24.8)
Missing	6,329 (1.6)	6,083 (1.6)	246 (1.5)
MATERNAL CHARACTERISTICS			
Age (years) at delivery:			
Mean (SD)	27.4 (6.2)	27.4 (6.2)	27.6 (6.1)
Missing: n (%)	2,186 (0.5)	1,381 (0.4)	805 (8.9)
Parity[¥]: n (%)			
0	252,267 (61.9)	242,736 (62.1)	9,531 (61.9)
1	108,157 (26.6)	103,789 (26.6)	9,531 (26.2)
2	34,426 (8.5)	33,032 (8.5)	1,394 (8.4)
≥3	11,666 (2.9)	11,071 (2.8)	595 (3.6)
Missing	826 (0.2)	60 (0.02)	766 (4.6)
Maternal death by child age 2 years: n (%)	907 (0.2)	825 (0.2)	82 (0.5)

[¥]This proportion includes children who had data inconsistencies

Abbreviations – SD: standard deviation