Meyers, T., et al. (2012). Changes in paediatric HIV-related hospital admissions and mortality in Soweto, South Africa 1996-2011: light at the end of the tunnel? JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME, 60:503–510

Changes in paediatric HIV-related hospital admissions and mortality in Soweto, South Africa 1996-2011: light at the end of the tunnel?

Tammy Meyers, MD, Angela Dramowski, MD, † Helen Schneider, MD, ‡ Nicolene Gardiner, MD, §Louise Kuhn, MPH, PhD, \\ ¶ and David Moore, MD#*

Background: With widespread availability of pediatric antiretro- viral therapy and improved access to prevention of mother-to-child transmission (PMTCT), it is important to monitor the impact on pediatric HIV-related hospital admissions and in-hospital mortality in South Africa.

Methods: Over a 15-year period, 4 independent surveillance studies were conducted in the pediatric wards at Chris Hani Baragwanath Hospital in Soweto, South Africa (1996, 2005, 2007, and late 2010 to early 2011). Trends in HIV prevalence and HIV-related mortality were evaluated.

Results: HIV prevalence was similar during the first 3 periods: 26.2% (1996), 31.7% (2005), and 29.5% (2007) $P > 0.10$, but was lower in 2010-2011 (19.3%; $P = 0.0005$). Median age of the children admitted with HIV increased in the latter periods from 9.13 (interquartile range 3.6-28.8) months to 10.0 (3.0-44.5) months ($P > 0.10$) and 18.0 (6.2-69.8) months ($P = 0.048$). Median admission weight-for-age z-scores were similar (< -3 SD) for the latter 3 periods. Admission CD4 percentage increased from 0.0% (0.0-9.4) in 2005 to 15.0% (8.2-22.8) in 2007 ($P < 0.0001$) and was 18.7% (9.6-24.7) in 2010-2011 ($P > 0.10$). Mortality among all vs. HIV-infected admissions was 63 of 565 (11.2%) and 43 of 179 (24.0%) in 2005, 91 of 1510 (6.0%) and 53 of 440 (12.0%) in 2007, and 18 of 429 (4.2%) and 9 of 73 (12.3%) in 2010-2011.

Conclusions: HIV prevalence and mortality among pediatric admissions is decreasing. This is likely a result of improved PMTCT and wider antiretroviral therapy coverage. Continued effort to improve PMTCT coverage and identify and treat younger and older HIV-infected children is required to further reduce HIV-related morbidity and mortality.

Key Words: pediatric HIV, admissions and mortality, changes over time, Soweto South Africa

From the *Department of Paediatrics, Harriet Shezi Clinic, Chris Hani Baragwanath Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; †Academic Unit for Infection Prevention and Control, Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa; ‡School of Public Health, University of the Western Cape, Cape Town, South Africa; §AURUM Institute, Johannesburg, South Africa; || Gertrude H. Sergievsky Center, College of Physicians and Surgeons; ¶Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; and #Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases & Medical Research Council, Respiratory & Meningeal Pathogens Research Unit, University of the Witwatersrand, Soweto, South Africa.

Correspondence to: Tammy Meyers, MD, Department of Paediatrics, Chris Hani Baragwanath Hospital, PO Bertsham 2013, Johannesburg, South Africa (e-mail: tammy@meyers.net).

INTRODUCTION

By the end of 2009, there were an estimated 330,000 children infected with HIV in South Africa, accounting for 13.2% of the world's HIV-infected children.[1] In the same year, it was estimated that up to 35% of deaths among South African children younger than 5 years were HIV related.[2] Prevalence of HIV among admissions to pediatric wards has been tracked and used as a marker of the impact of HIV on health services for children. At Chris Hani Baragwanath (CHB) Hospital, in Soweto, South Africa, the trends in HIV prevalence among pediatric admissions have been intermittently evaluated over a 20-year period. Between May and April 1990, 23 children were diagnosed with HIV at the hospital (the first cases described at this institution).[3] Following a rapid rise in HIV prevalence among pregnant women,[4] Zwi et al[5] reported that HIV-related pediatric admissions climbed from 1% to almost 30% of all admissions from until 1996. In-hospital mortality increased by 42% during this period, attributable to HIV.[6]

Provision of antiretroviral therapy (ART) for adults and children by the South African National Department of Health began in 2004. Before this, few children had access to ART. Uptake among children was initially slow, but South Africa now has the largest ART program globally with an estimated pediatric ART coverage of 54% in 2010.[2] Despite lengthy delays in implementing HIV prevention of mother-to-child transmission (PMTCT) programs in South Africa, there is now evidence that vertical transmission of HIV is decreasing. Data from the National Health Laboratory Services on HIV DNA polymerase chain reaction (PCR) test positivity rates for HIV-exposed children attending government clinics show a decline among HIV-exposed infants younger than 2 months from 8.2% to 4.3%, and estimated coverage of early infant testing (within 2 months of birth) improved from 31.4% to 54.7%.[7] A study evaluating the effectiveness in 2010 of the national PMTCT program showed that among 9915 infants attending government clinics across the country for first immunization, 31.4% were HIV -exposed, and the HIV transmission rate from mother-to-child was 3.5% in these infants aged 4-8 weeks.[8]

Based on these programmatic improvements, with declining vertical HIV transmission and increasing pediatric ART coverage, we describe the impact on HIV prevalence and inpatient mortality among children admitted to the pediatric wards at CHB hospital.

MATERIALS AND METHODS

CHB hospital, one of the largest public hospitals on the African continent, serves a population of 1.4 million in Soweto, Johannesburg, in the Gauteng Province of South Africa. The hospital is a referral center for local primary health care clinics, regional hospitals in Gauteng, and neighboring provinces. Approximately 6000 children up to age 15 years are admitted annually. PMTCT services are widespread in the Soweto area, and the Harriet Shezi Children's Clinic at CHB provides outpatient pediatric HIV services for children from the Soweto area and surrounds. Almost 5000 children have initiated ART since 2004, of whom more than 1200 have been out referred to district services for ongoing care and treatment.

Table 1 summarizes study design, study population, timing, and HIV diagnostic criteria applied for 4 surveillance studies included in this analysis and conducted in the pediatric wards of CHB between 1996 and 2011. Approval to conduct each surveillance study and to compare them over time was obtained from the Human Research Ethics Committee of the University of the Witwatersrand.

TABLE 1. Summary of 4 Surveillance Studies Conducted at CHB, 1996–2011

Period	PMTCT Available	Wards Included	Duration, mo	Sample Size	Season	Prospective	Age of Children, y	Age at Diagnosis of HIV ELISA vs. DNA PCR, mo
July 1 to December 31, 1996[10]	None	1 of 4	6	549	Winter to summer	Yes	<5	15
April 18 to May 15, 2005[11]	CD4 < 200 cells/mm3 → ART start mother CD4 > 200 cells/mm3 → single-dose nevirapine for mother and baby	All four	1	575	Autumn	Yes	<15	15
October 1 to December 31, 2007[12]	CD4 < 200 cells/mm3 → ART start mother CD4 > 200 cells/mm3 → single-dose nevirapine for mother and baby	All four	3	1510	Spring to summer	No	<15	18
August 1, 2010, to January 31, 2011	CD4 < 350 cells/mm3 → ART start mother CD4 > 350 cells/mm3 → AZT from 14 wks and single-dose nevirapine for mother and baby	1 of 4	6	429	Winter to summer	Yes	<15	18

ELISA, enzyme-linked immunosorbent assay.

During this period, the HIV/AIDS program in South Africa underwent several changes. In 2003, a constitutional court order compelled the government to provide single- dose nevirapine as part of a national PMTCT program. In early 2004, a government-led program providing universal access to ART was introduced in South Africa. Initially, World Health Organization' s (WHO) ART guidelines were used, but these had scant guidance for treatment of children, especially for the care of young infants. By 2008, it became evident from the Children with HIV Early Antiretroviral Therapy study that HIV-related deaths in infants and young children could be dramatically reduced by early ART.[9] As a result, WHO revised guidelines recommending that all infants with HIV infection start ART early in the first year of life. During this period, the South African-Expanded Program on Immunization (EPI) introduced new vaccines (*Haemophilus influenzae* type b in 1999 and pneumococcal and rotavirus vaccines in 2009). In the earlier periods, HIV testing was mainly offered to children presenting for admission with signs and symptoms of HIV disease. The practice of provider-initiated counseling and testing was formally implemented in 2010 when a government policy document on counseling and testing was published, stipulating that all adults and children presenting at health services should be offered HIV testing.[13]

Methodology of the Most Recent Study (2010/2011)

From August 1, 2010, through January 31, 2011, children were enrolled prospectively from 1 of 4 general pediatric wards. Admissions to 1 ward are representative of pediatric admissions to the hospital because patients are admitted to each of 4 wards on a cyclical basis. Provider- initiated counseling and testing for all pediatric admissions is part of routine care. Where HIV status was unknown, parental consent for testing was obtained. Only data from children whose caregivers (parents or guardians) consented to use of hospital data were included in the analysis.

HIV infection was defined as HIV antibody positive in children 18 months and older or HIV PCR positive in children younger than 18 months. HIV uninfected was defined as HIV antibody negative for children 18 months and older and DNA PCR negative in children younger than 18 months or HIV antibody negative in children younger than 18 months or their mothers, indicating lack of HIV exposure. HIV status was recorded as unknown if the test result was not found.

Data were collected from hospital discharge and death summary forms that are routinely completed by hospital staff. Each admission was regarded as a separate event. However, to assess the number of unique patients admitted and calculate mortality rates, patients readmitted during the study period were only counted once.

Methodology for Previous Studies 2007

A cross-sectional retrospective review of all children (from birth to 14 years of age) admitted to all 4 general pediatric wards at CHB between October 1, 2007, and December 31, 2007, was performed. HIV status was determined by review of laboratory and/or hospital records. HIV diagnosis was established using the criteria as described above for 2010/11. HIV period prevalence was calculated using all admissions in the study sampling time frame as the denominator and in-hospital mortality rates using hospital records and routinely collected pediatric ward mortality data. In-depth data on the profile of HIV-infected pediatric admissions were extracted from individual patient records that were available for 440 of the 446 HIV-infected children.[12]

2005

As part of a larger sentinel surveillance study to monitor the impact of HIV on health services in Gauteng Province, information was collected on all patients admitted to the medical and pediatric wards of 4 selected hospitals over a 4- to 6-week period in April and May 2005. The CHB hospital's pediatric wards were included among the sites targeted for surveillance, and children were enrolled from all general pediatric wards at CHB. Consent for recording of clinical and demographic information into structured study case report forms, and HIV testing (if status was not already known), was obtained from caregivers. Discharge summaries were completed by ward doctors.

At the time of conduct of this study, the cutoff for enzyme-linked immunosorbent assay positivity as an indicator of vertical acquisition of maternally derived antibody was 15 months. HIV infection was defined as being confirmed in children 15 months and older with positive antibody tests or in children younger than 15 months if a positive PCR result was obtained. Children younger than 15 months of age with a positive antibody test and clinical evidence of HIV infection but no confirmatory PCR (exposed with clinical evidence) or children of any age without any evidence of an HIV test result but who were suspected of having HIV infection on clinical grounds were deemed to be HIV infected.[11]

1996

From July 1, to December 31, 1996, children younger than 5 years admitted to 1 ward at CHB were enrolled. Parental consent for testing was sought. HIV antibody testing was used to screen patients. Children with positive results had confirmatory serologic tests performed if they were 15 months and older and DNA PCR testing if younger than 15 months and asymptomatic for HIV. Children younger than 15 months with positive HIV serology and clinical features of HIV infection were deemed to be HIV infected. Each admission was regarded as a separate event for most of the analyses; however, to assess the number of first admissions and mortality rates, patients readmitted during the study period were only counted once. Patients were enrolled from 1 ward over a 6-month period. This study only included children up to 5 years of age.[10]

Statistical Methods

Proportions and descriptive statistics were calculated for each survey. Groups were compared within surveys and between surveys using x^2 tests for categorical outcomes and Wilcoxon tests for continuous outcomes.

RESULTS

From 1996 until 2007, HIV prevalence among children hospitalized at CHB remained relatively constant: 26.2% (1996; children younger than 5 years), 31.7% (2005), and 29.5% (2007), $P > 0.10$, but was significantly lower (19.3%) by 2010-2011 ($P = 0.0005$; Table 2).

Of the children admitted in 2010-2011, 429 of 564 children (76.1%) had caregiver consent to use their hospital information for study purposes. In this period, there were 397 unique children admitted (32 of 429 had repeat admissions), 308 (HIV uninfected 77.6%), 73 HIV infected (18.4%), and 16 (4.0%) of unknown HIV status.

The median age of the HIV-infected children in the 2010-2011 study was significantly older than the HIV- uninfected group: 18.0 vs. 7.3 months ($P < 0.0001$) with 20 of 73 (27.4%) vs. 51 of 308 (16.6%; $P = 0.002$) older than 60 months (Table 3). HIV-infected children were significantly more malnourished than their HIV-uninfected counterparts with median WAZ score -3.48 vs. -1.26 ($P < 0.0001$). Pneumonia 23 of 73 (31.5%), tuberculosis (TB) 18 of 73 (24.7%), urinary tract infections 15 of 73 (20.5%), and gastroenteritis 14 of 73 (19.2%) were the most common diagnoses among HIV-infected children, who had longer duration of hospitalization than HIV-uninfected children (10 vs. 6 days, $P < 0.0001$) and higher in-hospital case fatality rates [9 of 73 (12.3%) vs. 7 of 308 (2.3%), $P = 0.0001$).

Among HIV-infected admissions during the 2005, 2007, and 2010-2011 studies, the age profiles of children changed with 40.1% (2005), 37.7% (2007), and 24.7% (2010-2011) of children being younger than 6 months when admitted (Table 4). The proportion of children admitted over 5 years of age also increased from 15.9% (2005) to 22.3% (2007) and 27.4% (2010-2011). Median WAZ score was similar over the 3 periods. Median CD4% increased from 0.0 [interquartile range (IQR), 0.0-9.4; 2005] to 15.0 (IQR, 8.2-22.8; 2007) ($P < 0.0001$) and 18.7% (IQR, 9.6-24.7; 2010-2011) ($P > 0.10$). The proportion of HIV-infected children already established on ART at the time of hospitalization increased steadily, from 22 of 182 (12.1%; 2005) to 76 of 440 (17.3%; 2007) and 26 of 73 (35.6%; 2010-2011).

TABLE 2. Prevalence of HIV and Mortality Rates Among Pediatric Admissions in 4 Surveillance Studies Conducted at CHB, Soweto, South Africa, 1996–2011

Period	Ward	Age Range, y	No. Children Included of Total Admissions (%)	Number With HIV Infection (%)*	Percentage With Unknown HIV Status	Mortality Rate Among All Admissions (%)
June 1 to December 31, 1996	1 of 4	0–5	549/549 (100.0)	144/549 (26.2)	56/549 (10.2)	32/493 (6.5)†
April 18 to May 15, 2005	All four	0–15	575/615 (93.5)	182/575 (31.7)	37/575 (6.4)	64/575 (11.1)
October 1 to December 31, 2007	All four	0–15	1510/1510 (100.0)	446/1510 (29.5)	227/1510 (15.0)	91/1510 (6.0)
August 1, 2010 to January 31, 2011	1 of 4	0–15	429/564 (76.1)	83/429 (19.3)	16/429 (3.7)	18/429 (4.2)

*$P < 0.0001$ comparing the HIV prevalence between all 4 studies and $P > 0.10$ comparing only the first 3 studies.
†Number of deaths refers to those among the HIV-infected and HIV-uninfected children only. Number of deaths among HIV unknown group not reported.

Between 2007 and 2010-2011, the frequency of in-hospital ART initiation increased from 15 of 364 (4.1%) to 11 of 47 (23.4%) ($P < 0.0001$). There are no data indicating whether children were initiated on ART in the 2005 period.

TABLE 3. Profile of 397* Children Admitted to CHB During the Most Recent Surveillance Study (2010–2011) by HIV Status

	HIV Infected (n = 73)	HIV Uninfected (n = 308)	HIV Unknown (n = 16)	*P* (HIV Infected vs. Uninfected)‡
Median age, mo	18.0	7.3	23.5	<0.0001
<6	18 (24.7)	143 (46.4)	4 (25.0)	0.003
6 to <24	25 (34.3)	67 (21.8)	4 (25.0)	
24 to <60	10 (13.7)	47 (15.3)	4 (25.0)	
>60	20 (27.4)	51 (16.6)	4 (25.0)	
Sex (% female)	27 (37.0)	129 (41.9)	7 (43.8)	>0.10
Median weight-for-age *z* score (IQR)†	−3.48 (−4.38 to −1.56; n = 67)	−1.26 (−2.47 to −0.20; n = 289)	−1.30 (−3.33 to −0.60; n = 13)	<0.0001
Most frequent admission diagnosis (%)	Bronchopneumonia: 23 (31.5)	Bacterial sepsis of the newborn: 53 (17.2)	Gastroenteritis: 4 (25)	
Second most frequent admission diagnosis (%)	Primary pulmonary TB: 18 (24.7)	Bronchopneumonia: 47 (15.3)	Bacterial sepsis of the newborn: 3 (18.8)	
Third most frequent admission diagnosis (%)	Urinary tract infection: 15 (20.5); gastroenteritis: 14 (19.2)	Gastroenteritis: 45 (14.6)	Bronchopneumonia: 2 (12.5)	
Median length of hospital stay, d	10	6	5.5	<0.0001
No. died (%)	9 (12.3)	7 (2.3)	2 (12.5)	0.0001

*Unique children only (32 repeat hospitalizations are excluded).

†Children younger than 10 years: 6 HIV-infected, 18 HIV-uninfected, and 3 HIV-unknown children were older than 10 years and were not included in the comparison as WHO Growth Reference Standards software only accommodates analysis up to 10 years of age. One child in the HIV-uninfected group had no recorded weight.

‡Categorical variables were compared using χ^2 tests and continuous variables using Wilcoxon test.

Number of deaths refers to those among the HIV-infected and HIV-uninfected children only. Number of deaths among HIV unknown group not reported.

TABLE 4. Comparisons of Characteristics of the HIV-infected Children Admitted to CHB in 3 Surveillance Studies; 2005, 2007 and 2010–2011

	Children Admitted April 18, to May 15, 2005 (n = 182)	Children Admitted October 1, to December 31, 2007 (n = 440)	Children Admitted August 1, 2010, to January 31, 2011 (n = 73)	*P** (2005 vs. 2007)	*P*† (2007 vs. 2010–2011)
Sex: female (%)	89 (48.9)	206 (46.8)	27 (37.0)	>0.10	>0.10
Median age (IQR), mo	9.13 (3.6–28.8)	10.0 (3.0–44.5)	18.0 (6.2–69.8)	>0.10	0.048
<6 (%)	73 (40.1)	166 (37.7)	18 (24.7)	0.578	0.031
6 to <24 (%)	54 (29.7)	116 (26.4)	25 (34.3)	0.400	0.162
24 to <60 (%)	26 (14.3)	60 (13.6)	10 (13.7)	0.831	0.989
>60 (%)	29 (15.9)	98 (22.3)	20 (27.4)	0.074	0.335
Median WAZ score (IQR)*	−3.08 (−4.40 to −1.77; n = 173)	−3.05 (−4.15 to −1.68; n = 402)	−3.48 (−4.38 to −1.56; n = 67)	>0.10	>0.10
Median CD4% (IQR)	0.0 (0.0–9.4)	15.0 (8.2–22.8)	18.7 (9.6–24.7)	<0.0001	>0.10
Number started ART at current visit (%)	Not available	15/364 (4.1)	11/47 (23)	—	<0.001
Number already on ART (%)	22/182 (12.1)	76 (17.3)	26 (35.6)	>0.1	0.0003

*Children younger than 10 years.

†Categorical variables were compared using χ^2 tests and continuous variables using Wilcoxon test.

TABLE 5. Mortality by Surveillance Study Period Among All Pediatric Admissions (2005–2011), by HIV Infection Status, Percent Deaths of HIV-Infected Infants Younger than 6 Months, and Percent HIV-Related Deaths

	April 18, to May 15, 2005 (n = 565)	October 1, to December 31, 2007 (n = 1510)	August 1, 2010 to January 31, 2011 (n = 397)
Mortality rate overall (%)	63/565 (11.2)	91/1510 (6.0)	18/429 (4.2)
Mortality in HIV uninfected (%)*	16/350 (4.6)	38/1064 (3.6)‡	7/308 (2.3)
Mortality in HIV infected (%)†	43/179 (24.0)	53/440 (12.0)	9/73 (12.3)
Deaths in HIV-infected children <6 months by all deaths <6 months	18/27 (66.7)	28/40 (70.0)	4/9 (44.4)
Percentage of all deaths that were HIV related	43/63 (68.3)	53/91 (58.2)	9/18 (50.0)

*Not significantly different across time ($P > 0.10$).
†P 0.001 for difference over time (χ^2 test for trend).
‡This number includes deaths in HIV-uninfected, HIV-exposed unknown, and HIV-unknown children.

Mortality rates decreased over the latter 3 periods (Table 5). Among HIV-infected children, mortality rates declined from 24.0% (2005) to 12.0% (2007) and 12.3% (2010-2011). There was no significant change in mortality among HIV-uninfected children over the different study periods. HIV-attributable deaths among infants younger than 6 months were 66.7% (18 of 27; 2005), 70.0% (28 of 40; 2007) decreasing to 44.4% (4 of 9; 2010-2011). HIV prevalence among children who died ranged from 68.3% (2005) and 58.2% (2007) to 50.0% in the 2010-2011 study.

Infectious diseases were the most common diagnoses among those who died, with pneumonia being the most common cause of death in all study periods. Death was attributed to TB in 18.0%, 26.3%, and 44.0% of children in 2005, 2007, and 2010-2011, respectively (data not shown).

DISCUSSION

This number includes deaths in HIV-uninfected, HIV-exposed unknown, and HIV-unknown children.

The results presented here demonstrate an encouraging trend in the pattern of HIV-related pediatric admissions and overall mortality at one of the busiest public hospitals in South Africa. Despite wide availability of PMTCT and ART services in South Africa since the early part of this century, it is only in the most recent study at CHB hospital that HIV- related admissions have decreased. HIV prevalence among pediatric admissions seems to have peaked (31.7%) in 2005 decreasing to 19.3% (2010/2011).

Previous reports on child health in South Africa have painted a bleak picture of the effect HIV has had on childhood morbidity and mortality. Over the last 2 decades, with the burden of HIV increasing sharply among pregnant women, pediatric hospitalizations increased simultaneously, mirrored by rising pediatric mortality. South Africa's under 5 mortality (U5M) rate in 1990 was 56 per 1000 live births, rising to 73 and 67 per 1000 live births in 2000 and 2008, respectively.[14] This reversal in downward U5M trends was attributable to the pediatric HIV epidemic.[15]
The results of our study reflect progress due to several factors. Nationwide vertical HIV transmission rates have declined consequently on recent improvements to the PMTCT programs.[7,8] Thousands of HIV-infected children are now accessing ART, with excellent outcomes reported at the HIV outpatient service at CHB[16] and from pooled data from multicenter sites in South Africa.[17] In a recent report on Sowetan children admitted to CHB, a significant reduction in invasive pneumococcal disease among HIV-infected children over the period 2003-2008 was described. Because this was before pneumococcal conjugate vaccine (PCV) being introduced, the authors attribute this to increasing ART coverage among children.[18] Together, reduction in perinatal HIV transmission and wider ART coverage likely account for the

reduction in HIV-related admissions and for some of the improvement in mortality rates among children admitted to the hospital.

Coverage of adult antiretroviral treatment services has also improved. One report from rural South Africa suggests that maternal ART improves outcomes in their offspring.[19] This may also be a potential explanation for the improving child outcomes that we observed.

During the period spanned by the surveys reported here, new vaccines were introduced into the South African immunization program. Introduction of *H. influenzae* type b vaccine in 1999 was associated with a significant reduction in the number of cases of invasive *H. influenzae* type b dis- ease,[20] and despite the vaccine being reportedly less immunogenic in HIV-infected children in South Africa, it was still estimated to be 83.2% effective.[18] In April 2009, PCV was introduced into the EPI and significant reductions in morbidity and mortality attributable to *Streptococcus pneumoniae* have been reported.[21,22] Although PCV is less effective in HIV-infected children, the vaccine has effected a marked reduction in invasive pneumococcal disease because of the disproportionate burden of pneumococcal disease encountered in this immunosuppressed group of children.[23] Additionally, oral rotavirus vaccine was introduced into the EPI in 2009. Rotavirus infection is considered to be the leading cause of dehydrating diarrheal diseases globally. Oral rota- virus vaccine has demonstrated efficacy in reducing the burden of diarrheal disease and, although less effective, has demonstrated immunogenicity and is well tolerated in HIV- infected children.[24]

The contribution of TB to morbidity and mortality among HIV-infected children increased during the period. This may partly reflect a proportional decrease in illness from vaccine-preventable acute respiratory infections, prevented by introduction of new vaccines. It is however plausible that this trend may reflect an absolute increase in TB prevalence, possibly through increased household exposure or through increased risk for the development of TB immune reconstitution inflammatory syndrome (IRIS) in the latter periods. TB IRIS was diagnosed in 10 of 296 children starting antiretroviral in Cape Town, 2003-2005.[25] In the NEVEREST study (2005-2006), 34 of 162 children with IRIS included 24 with Bacille Calmette-Guerin and 12 TB IRIS.[26] With rising numbers of children starting ART in South Africa, increased vigilance for TB IRIS is warranted. We did not have data on the proportion of deaths attributable to culture-confirmed TB in the various studies, although culture-confirmed disease in children is rare. Improved tools for TB diagnosis (GeneXpert) were unavailable and only subsequently introduced in the hospital. Because there was no change in diagnostic methods for pediatric TB, this is unlikely to explain the rise in TB-related mortality in the later periods. Empirical diagnosis of TB may have been more frequently considered in children subsequent to the publication of the WHO TB guidance document in 2006.[27] It has been demonstrated that there is a high prevalence of drug-resistant *Mycobacterium tuberculosis* amongst children diagnosed with culture-confirmed TB at CHB,[28] which may have contributed to more severe illness as a consequence of poor response to first-line anti-TB therapy. Our findings emphasize that TB remains an important coinfection in children with HIV. Efforts to prevent TB disease and death should focus on the use of isoniazid preventive therapy, early diagnosis, and treatment of TB.

The declining proportion of HIV-attributable deaths among the very youngest infants is also heartening. Young infants are most vulnerable to HIV-related death, as demonstrated by Bourne et al,[29] where deaths among young infants caused the sharp spike in South Africa's infant and U5MR between 1997 and 2002. If, as suggested by our study, mortality in this age group is falling, then we cautiously anticipate a reduction in infant and U5 mortality rates and movement in the right direction to attain the fourth Millenium Development Goal of a two-thirds reduction in U5M by 2015.[30]

An interesting finding in our study was that median age of children admitted with HIV to the hospital increased in the 2010-2011 period. The likely explanation for this is that, as the PMTCT

program expands and fewer infants become infected,[7] the burden of HIV disease among young infants is starting to decrease. HIV infection in women rose rapidly in the late 1990s and early 2000s, resulting in HIV transmission to a large numbers of infants in the absence of a functional PMTCT program. Although many infants likely presented and died early, survivors and long-term progressors may have remained undiagnosed, becoming sick and requiring admission for the first time at older ages and in the later study periods. A study on temporal trends, among children treated at multiple centers in South Africa, demonstrated that between 2004 and 2009, although the proportion of children younger than 18 months starting ART increased, the median age of children starting ART rose.[31] In addition, recent modeling by Marston et al[32] using pooled multicenter data suggests that mortality is significantly delayed among infants acquiring HIV postnatally through breast-feeding vs. infants infected perinatally. Although replacement formula feeding has been available to infants of HIV-infected women, many may not have accessed this intervention and mixed formula and breast-feeding occurred commonly.[33]

Children being admitted and diagnosed for the first time at older ages may reflect some of these dynamics. It is important for health care providers to be vigilant for signs of HIV among older children. Of particular note in this regard is the relatively high proportion (15%) of children who remained HIV unknown in the only retrospective survey described in this article (2007), which possibly reflects the prevailing practice of HIV testing of admitted children at the time of that survey.

There are several limitations to this study. No uniform surveillance system was in place at the hospital, and all the surveys were conducted using different methodologies, making direct comparison of the studies challenging. In the period 2010-2011, a larger proportion of caregivers did not sign consent for their children's hospital information to be used as part of the study and the sample size in the latest period was the smallest. The reason for the higher rate of exclusion in the latter period was due to budgetary constraints that precluded having study staff available to obtain consent at all times. Consent for participation was missing not because of active refusals but because caregivers were not available to provide consent at times when study personnel attended the wards. It is unlikely that this resulted in bias to the proportion of HIV admissions or mortality in this latter period. Although reasons for admissions and deaths were available, there was insufficient detail to establish whether these were IRIS related or in any way associated with ART. The results from this large urban academic hospital, in the well-resourced province of Gauteng, may not be directly generalizable to rural or less well-resourced settings. Nevertheless, we believe that each study period is representative of admissions to the hospital during that time because each survey used a representative sample of admissions to the general pediatric wards at the facility. Our results are cause for cautious optimism for both our immediate environment and for other settings in South Africa, and because the PMTCT program is widely implemented, there is broader access to ART for HIV-infected children, and the new EPI vaccinations are available nationally.

There is, however, little room for complacency. Nearly one-fifth of the estimated 6000 admissions to the pediatric wards at CHB remain HIV related in 2010-2011. Even though results from the PMTCT program are reassuring, HIV is a preventable condition in children, and most cases should be successfully prevented. Among HIV-infected infants for whom PMTCT has failed, HIV diagnosis and access to ART is often delayed until the first episode of hospitalization. PMTCT and ART coverage needs to continue to grow and expand, to ensure that fewer opportunities for intervention are missed. Mortality remains greater in HIV- infected children than their uninfected counterparts. A high index of suspicion for HIV infection should be maintained, and routine HIV screening of all children presenting at health services should increase to diagnose all infants and older children. With continued effort, South Africa can regain some ground in attaining the fourth Millenium Development Goal target and substantially reduce new HIV infections and HIV-related deaths among children.

ACKNOWLEDGMENTS
The authors are grateful to Chih-Chi Hu of the Gertrude H. Sergievsky Center, College of Physicians and Surgeons, and Department of Epidemiology, Mailman School of Public Health, for her insightful assistance with statistical analysis.

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