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VACCINATION DROPOUT IN SOUTH AFRICA

Ben Mabaleka Chavula

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Science in Medicine in the field of Vaccinology

Johannesburg, South Africa, September 2022

Declaration

I, Ben Mabaleka Chavula, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the field of Vaccinology at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted previously for any degree or examination at this or any other university.

Signature: 

Date: 23rd September 2022

Place: Johannesburg, Republic of South Africa

Dedication

I dedicate this work to my wife, Virginia Chavula, for your patience, untiring support and love. You supported my decision to undertake the course, despite knowing the sacrifice this would have on our family. Thank you for your understanding.

To my son, Ntchindi, who was born as I undertook the course, you are a big source of motivation and the light of our family.

To my parents, Bernard and Ethel Chavula, thank you for your unconditional love and support through so many years. I will always remain thankful.

To my siblings, Rachel, Blessings, Glory, Davie and Faith, thank you for always being around and supportive on numerous occasions!

The future belongs to those who believe in the beauty of their dreams.

-Eleanor Roosevelt

Abstract

Background: Vaccination is one of the most effective public health interventions. However, vaccine efficacy is dependent on completeness and timeliness of vaccine doses. Using data from the South African national vaccination coverage survey completed in 2019, we assessed vaccination timeliness, dropout rates and reasons for missed doses in three provinces of South Africa.

Methods: This study was a descriptive cross-sectional study including children aged 24-35 months in Gauteng, KwaZulu-Natal and Eastern Cape provinces in South Africa. Timeliness was calculated for each dose received by the child in reference to their date of birth while dropout rate was calculated as the proportion of children who received an earlier vaccine dose, but not the later dose. Analyses were done on the following vaccines; Bacillus Calmette-Guérin (BCG), each of the 3 doses of diphtheria-pertussis-tetanus (DPT) containing vaccine (hexavalent1, 2 and 3), and 2 doses of measles-containing vaccine (MCV1 and MCV2). Data analysis was done using STATA 15.

Results: 1,827 children aged 24-35 months were included in the analysis; 687 (37.6%) from Gauteng, 872 (47.7%) from KwaZulu-Natal and 268 (14.7%) from Eastern Cape. Timely vaccination coverage ranged from the lowest of 55.4% for MCV2 given at 12 months, to the highest of 92.9% for BCG given at birth. There was a trend towards increased vaccination delay with the vaccines administered later in life, with vaccination delay ranging from 5.7% for BCG to 25.0% for MCV2. Specific dropout rate between hexa1 and hexa3, and between MCV1 and MCV2 were 2.1% and 5.3% respectively. Over 8% of children who received BCG vaccine failed to complete their vaccination schedule with MCV2. For children who missed vaccines, at least 1 in 5 instances, the child was taken to the health facility, but a vaccine stock-out had occurred. There were substantial differences in vaccination timeliness and dropout rates at provincial level, with Gauteng having the highest proportion of children vaccinated on time while a high proportion of doses delayed and the highest vaccination dropout rates was noted in Eastern Cape.

Conclusions: Vaccination timeliness and dropout remain a concern in EPI-SA, with significant variation by province. The NDoH, EPI-SA and relevant stakeholders, need to use the timeliness and dropout rate indicators to implement interventions that address the major bottlenecks in immunization programs. Such interventions include catch-up vaccination campaigns for those missed or dropped from schedule, interventions to increase demand and timely uptake of vaccines.

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Abbreviations and acronyms

BCG	Bacille Calmette Guérin
DHS	Demographic and Health Survey
DPT	diphtheria, tetanus, pertussis
DTaP	diphtheria, tetanus, acellular pertussis
EPI	Expanded Program on Immunization
EPI-SA	South African Expanded Program on Immunization
FIC	Fully Immunised under one year old Coverage
GVAP	Global Vaccine Action Plan
HepB	hepatitis B
Hexa1	First dose of a hexavalent combination vaccine (diphtheria, tetanus, pertussis (DTaP vaccine); *Haemophilus influenzae* type b (Hib vaccine); inactivated polio vaccine [IPV]); hepatitis B (HepB vaccine))
Hexa2	Second dose of a hexavalent combination vaccine
Hexa3	Third dose of a hexavalent combination vaccine
Hib	Haemophilus influenzae type b
HREC	Human Research Ethics Committee, RSA
IPV	Inactivated polio vaccine
LMICs	Low- and Middle-Income Countries
MCV1	First dose of a measles-containing vaccine

MCV2	Second dose of a measles-containing vaccine
NDoH	National Department of Health, RSA
OPV	oral polio vaccine
PCV	pneumococcal conjugate vaccine
Penta	pentavalent combination vaccine
RSA	Republic of South Africa
RTHC	Road-to-Health card
RV	rotavirus vaccine
SADHS	South African Demographic Health Survey
SAGE	Strategic Advisory Group of Experts on Immunization
SDG	Sustainable Development Goal
UNICEF	United Nations International Childrens Funds
VPDs	Vaccine Preventable Diseases
WHO	World Health Organization
WUENIC	WHO and UNICEF Estimates of National Immunization Coverage

1. INTRODUCTION

1.1. Background

Vaccination is one of the most efficient and cost-effective public health interventions. (WHO, 2014) However, global rates of vaccination remain suboptimal and vary greatly across countries with children in developing countries continuing to have limited access. At least 1 in 5 children lacking access to routine vaccines and about 1.5 million childhood deaths each year are attributable to vaccine preventable diseases (VPDs). (WHO, 2014) (WHO/UNICEF, 2014) (Naghavi, et al., 2015) The World Health Organisation (WHO) promotes childhood vaccination through the Expanded Program on Immunization (EPI), and recommends a number of vaccines and vaccination schedules. (WHO, 2020)

EPI programmes have been established in all countries, and have proved to be one of the most important strategies for improving child survival. However, the reported data on vaccination coverage, timeliness and dropout rate vary across countries and have been poor in Low- and Middle-Income Countries (LMICs), possibly due to multiple barriers including poor service delivery and vaccine hesitancy. (WHO, 2015) (WHO, 2014) (WUENIC, 2020) The WHO Global Vaccine Action Plan (GVAP) 2011–2020 endorsed by all member states of the World Health Assembly earlier set a 2020 global target for countries to reach 90% national coverage of all their primary series vaccines. (WHO, 2013)

A systematic review and interpretive synthesis that looked at data in Low- and Middle-Income Countries (LMICs) had a framework that hypothesized three principal determinants of effective vaccination coverage and utilization that included; 1.Intent to vaccinate (acceptance and improved demand for vaccines by caregiver/parent), 2. facility readiness (adequate and consistent supply of vaccines and related supplies, and health workforce) and 3. Community access (ability to assess factors associated with vaccine utilization, this includes both the barriers and facilitators to vaccine uptake). (Phillips, et al., 2017)

1.2. Expanded Program on Immunization in South Africa

The South African Expanded Program on Immunization (EPI-SA), launched in 1995 by the National Department of Health (NDoH), initially provided free immunization services against six VPDs; tuberculosis, polio, diphtheria, tetanus, pertussis and measles and hepatitis B to children. Over time, new

and underutilized vaccines as recommended in World Health Organization (WHO) guidelines have been included in the schedule. (NDoH, 2015) Currently, a number of childhood vaccines are now routinely given in the EPI-SA to protect against the following infections: tuberculosis (Bacille Calmette Guérin [BCG] vaccine); polio (oral polio vaccine [OPV] or inactivated polio vaccine [IPV]); diphtheria, tetanus, pertussis (DTaP vaccine); *Haemophilus influenzae* type b (Hib vaccine); hepatitis B (HepB vaccine); rotavirus (rotavirus vaccine [RV]); *Streptococcus pneumoniae* (pneumococcal conjugate vaccine [PCV]); and measles (measles vaccine). (NDoH, 2015) (NDoH, 2019) The NDoH EPI-SA aims to ensure that at least 90% of all children are fully immunized by the age of one year. (NDoH, 2015) (NDoH, 2019)

Earlier data from South Africa confirmed that the administrative fully immunised <1 year old coverage (FIC) targets of the EPI-SA are not being reached. (Corrigal, et al., 2008) (Ndirangu, et al., 2009) (Fadnes, et al., 2011) Under ideal conditions, a perfect population adherence to the EPI-SA schedule would mean that every child receives all doses of every recommended vaccine on time. The EPI-SA has over time reported higher annual administrative coverage rates compared to that of WHO and United Nations Children's Fund (UNICEF) Estimates of National Immunization Coverage. (WUENIC, 2020) The South African Demographic Health Survey (SADHS) of 2016 reported an overall vaccination coverage of 61% among children aged 12-23 months, with lower coverage for girls than boys (59% versus 64%) and lower coverage in urban settings compared to non-urban settings (59% versus 65%). A decline in vaccination coverage for subsequent doses after the birth doses was also reported, with a decline from 92% for the birth dose of OPV, 91% for the first dose of DTaP-IPV-Hib, 86% for first dose of measles vaccine, and only 59% for the second dose of measles vaccine. (NDoH, 2019)

The results from the SADHS 2016 survey is also noted to differ significantly from the official results of 2016/2017 administrative estimates in the District Health Information System (DHIS), where an annual fully immunized under one year-old coverage estimate was reported to be above 80%. (Massyn, et al., 2017) Such differences in results from the SADHS, DHIS and WUENIC raised the need for a household based nationwide EPI coverage survey. In 2019, NDoH conducted South Africa's first large national household vaccination coverage survey powered to estimate vaccination coverage at district level in each of the 52 districts on South Africa. The survey aimed to investigate the following among children aged 24 to 35 months of age in South Africa: estimate vaccination coverage; measure the drop-out rates between vaccination dose series; measure vaccination timeliness; identify reasons for missed

vaccinations; and investigate the health system and personal predictors for and barriers to vaccination uptake. It aimed to visit 1.1 million houses in all 52 districts of South Africa so as to reach a targeted sample size of 55 120 children. (Burnett, et al., 2019a) (Burnett, et al., 2019b)

1.3. Indicators of EPI performance

Vaccination coverage is a core element in the assessment of EPI programme performance, but this does not address the important question of the timing when each scheduled vaccine dose was administered and if the child completed all the scheduled vaccines by the first or second birthday. Vaccination timeliness and dropout rates are indicators in assessing the quality of immunization programs in light of health equity. (Clark & Sanderson, 2009)

1.3.1. Vaccination timeliness

Vaccination timing refers to measures of vaccine uptake with some relation to time or date, depending on the recommended national EPI schedule. Such measures include; up-to-date vaccination (getting a vaccine by a specific age threshold), vaccination delay (vaccination after the vaccine's recommended age of administration) and vaccination timeliness (administration of a vaccine within a specified time from the defined recommended age of vaccination). (Masters, et al., 2019) Ensuring that children have access to the scheduled vaccines on time is a critically important and cost-effective model to decrease the incidence of disease and related morbidity and mortality within a population. Recent data from LMICs have indicated a disproportionately high burden of vaccine-preventable diseases, with a big impact among younger infants, and has thus proved that administration of vaccines at the recommended age as prescribed by the EPI programs is crucial. (Wahl, et al., 2018) A systematic review of 67 papers from LMICs concluded that the definition of what constitutes timely vaccination of a vaccine dose widely varies across settings, as such, a continuous measure of vaccine delay is advised to be used as is likely to provide more information and something that can easily be compared to. (Masters, et al., 2019) In this analysis, several studies were noted to have used different benchmarks of vaccination delay.

There has recently been a surge in number of studies that assessed vaccination timeliness. Some of the documented factors associated with inadequate vaccination timeliness include poor access or affordability, vaccine hesitancy and lack of knowledge and undestanding of the vaccines and the EPI recommended schedule by the caregiver/parents. (Thomson, et al., 2016) (WHO, 2014) The distribution

of determinants for vaccination delay has noted to vary across different settings with poor maternal education, low socioeconomic status, lacking reminders about next vaccination/clinic visit and home delivery been common in LMICs while the lack of health insurance and ethnicity mostly reported in High Income Countries (HICs). (Veerasingam, et al., 2017) (Tauil, et al., 2016)

1.3.2. Vaccination dropout rate

Vaccination dropout rate refers to the proportion of individuals that started their immunization series, but didn't finish it for some reason. (WHO, 2020). It is used to assess the need for supplementary vaccination to catch up missed doses. Delay and subsequent vaccination dropout is particularly dangerous as children may generally be at high risk for severe infection and death from VPDs. (Hamborsky, et al., 2021) In a recent study by Tang et al, it was noted that the overall coverages of routine vaccinations in Southwest China were high, but completeness were poor. (Tang, et al., 2021) Ensuring that parents/caregivers have a good knowledge and understanding of vaccines and immunization programs is one of the core elements in ensuring the success of the EPI programs. (Tabana, et al., 2016) As such, vaccinators need to be well trained to provide compelling information to caregivers/parents about vaccines and the EPI program. Such initiatives would likely improve acceptability among caregivers/parents and later lead to reduced dropout rates from the vaccination schedule. (Tabana, et al., 2016)

1.3.3. Methods of assessing EPI indicators

Assessment of vaccination coverage, timing and dropout rates can be done using data from any of the administrative (health facility level) records, road to health care cards (RTHC) and verbal recall. Administrative (Routine) data are the main data sources for monitoring and evaluating EPI programmes but these have limitations especially in Africa hence the need for community based EPI survey data which may provide high quality coverage data that can well be utilized for effective decision-making at all levels within the EPI. (Burton, et al., 2009) (Danovaro-Holliday, et al., 2018) Community based EPI surveys though vital for monitoring and evaluating immunization programs, have proved to be expensive and logistically challenging. (Burton, et al., 2009) (Danovaro-Holliday, et al., 2018) Community EPI survey data can be obtained from RTHC or verbal recall. However, as with all indicators, assessment may be biased towards higher coverage among children who possess a vaccination card compared to those without, as it requires well documented data on date of birth and date of vaccine administration

which are documented in the RTHC. However, retention of RTHC has proved to be a challenge in most LMIC, thus leading to reliance on verbal recall of dates by caregivers/parents. (Lakew, et al., 2015)

It is with this background that this study was conducted to asses the quality of South African EPI program in light of health equity by quantifying vaccination timeliness and dropout rates.

1.4. Factors associated with low uptake of vaccines

Several studies have documented a variety of factors that affect vaccination uptake. (Larson, et al., 2014) (WUENIC, 2020) (Burnett, et al., 2018) (Bangura, et al., 2020) (Landoh, et al., 2016) A study done in South Africa that analyzed 508 records collected from 2011 to 2014 found that supply chain, specifically vaccine stock-outs, were noted to contribute to 62% of missed vaccinations, showing that there is need to plan and implement strategies that ensure improved vaccine stock management at all levels. (Burnett, et al., 2018) A number of factors such as socio-economic, cultural and religious issues associated with vaccine hesitancy have been documented to contribute to incomplete vaccination, which varies across time, place and vaccine type. (WHO, 2014) (Larson, et al., 2014) (Burnett, et al., 2018)

A 2009 study had shown that a positive maternal HIV status was associated with under-vaccination hence also likely associated with childhood morbidity and mortality when compared to HIV-negative mothers. (Ndirangu, et al., 2009) However, these data were from a vertical HIV transmission study, as such, not very generalizable. Other reasons for under-vaccination included clinic-related factors (including being told by clinic staff to return another day due to vaccine stock-outs or after bringing a child on a day not scheduled for vaccination), lack of information, caregiver being unable to attend the clinic on the scheduled day for vaccination, and lack of motivation (Corrigal, et al., 2008) A systematic review by Bangura et al that included 48 studies from sub-Saharan African countries in the year 2020, described a number of factors associated with under-vaccination. The factors included long distance to vaccination site, distrust in vaccines and programs of immunizations, lack of money for bus fares or child care for other children remaining at home while the care-giver is out, lack of knowledge on immunization, migration and forgetfulness as cited by parents/caregivers. Limited health workforce, erratic supply of vaccines, inadequate infrastructure and limited cold chain system at the facility level were some of the notable health system challenges as cited by healthcare providers. (Bangura, et al., 2020) A study in Togo, where rates of incomplete vaccination among <5 year olds were reportedly high, reported that households headed by men and single mothers, poorly educated mothers and poor living

standards at household level were associated with vaccination dropout. (Landoh, et al., 2016) Similar findings were noted following analysis from the 2016 Ethiopian DHS and in a study carried out in Nigeria. (Tamirat & Sisay, 2019) (Duru, et al., 2016) The Togolese study further found that children from Muslim households were less likely to complete a vaccination series compared to children from Christian families. (Landoh, et al., 2016)

Furthermore, a recent study that analyzed data from 33 low- and middle-income countries (LMICs) in Africa reported that late vaccination in any dose series was significantly associated with failure to complete the EPI schedule by 12 months of age. (Janusz, et al., 2020) However, such studies are likely to have limitations in generalizability due to differences in EPI related programmatic challenges and barriers to access to vaccination services across countries in Africa. Social-cultural beliefs including a belief that vaccinating a girl child can lead to infertility later in life, a belief that vaccinating children at a very young age can be harmful, and ensuring that permission is sought from the mother-in-law prior to vaccinating a child have also been documented to affect vaccine uptake, likely leading to vaccination delay or failure to complete the vaccination schedule. (Mogoi, et al., 2019) A study that analyzed the 2015 Myanmar (formally Burma) DHS data found that pregnant women who seek maternal tetanus vaccination prior to giving birth, high maternal age and having had at least 4 antenatal care (ANC) visits were all associated with the full vaccination of their infants and this showed that mothers' acceptance of vaccines will most likely influence her decision to vaccinate her child. (Nozaki, et al., 2019) Improving the quality of the vaccination service such as ensuring a qualified health worker as a vaccinator and provision of adequate advice to the parents/caregivers relating to the benefits and safety of vaccines has been associated with improved vaccination uptake and completeness of the vaccination schedule. (Niang, et al., 2020)

1.5. Description of the Primary Study

The vaccination survey was conducted in 2019 and aimed to provide estimates of vaccination coverage of children aged 24 to 35 months of age at the national, provincial and district levels. It was conducted within each of the 52 districts in South Africa. The survey utilized a cluster survey design based on the WHO vaccination coverage cluster surveys reference manual and involved administration of a

questionnaire to mothers or caregivers of eligible children to acquire information on the immunization status of their children. (WHO, 2018)

The main objective of the survey was to estimate the proportion of children in South Africa, at national and district level, who are fully immunized with all the vaccines scheduled within the first year of life (up to and including the 3rd PCV dose scheduled at 9 months) and the second year of life (up to and including the 4th dose of DTaP-IPV-Hib-HepB scheduled at 18 months of age) at 5 % significance level (95% confidence interval) if the coverage is 65% or higher. Specifically, the survey aimed to estimate vaccination coverage among children 24 to 35 months of age at a representative district level; measure the drop-out rates between vaccination dose series; measure the timeliness of vaccinations; identify reasons for missed vaccinations; and investigate the health system and personal predictors for and barriers to vaccination uptake in South Africa.

1.6. Justification and objectives

1.6.1. Justification

Several studies assessing vaccination dropout rates and timeliness have been conducted in various settings and have yielded different results. However, there are limited data on dropout rates and timeliness in South Africa. It is with this background that the study was conducted to provide local empirical data. The differences in provinces may result in differences in indicators thus looking at 3 provinces, with varied demographics. The study was undertaken to quantify vaccination dropout and timeliness within the EPI-SA program utilizing the national EPI survey data. The results of this study will be useful in developing targeted interventions for policy and programme development and implementation in addressing vaccine dropouts and ensuring timeliness of vaccines. We hypothesized that the study would find a lower vaccine dropout rate compared to previous survey results in South Africa.

1.6.2. Aims

This study aimed to quantify vaccination dropout rates, timeliness and identify reasons given for missing a vaccine dose among children aged 24-35 months of age in Eastern Cape, Gauteng and KwaZulu-Natal

Provinces in South Africa using data collected during the national vaccination coverage survey conducted in 2019.

1.6.3. Objectives

The primary study objective was to measure vaccination dropouts and timeliness for the following scheduled vaccines; BCG at birth, hexa1 at 6 weeks of age, hexa2 at 10 weeks of age, hexa3 at 14 weeks of age, MCV1 at 6 months and MCV2 at 12 months, among children aged 24-35 months of age enrolled in the national vaccination coverage survey (July 2019- December 2019) in Eastern Cape, Gauteng and KwaZulu-Natal Provinces in South Africa during their first year of life.

1. To quantify vaccination dropout rates during their first year of life.
2. To assess timeliness of each vaccine dose.
3. To determine reasons given for missing a vaccine dose.

2. MATERIALS AND METHODS

2.1. Study Design

The study used a descriptive cross-sectional study design to estimate vaccination dropout rates and timeliness among children aged 24-35 months of age utilizing data from the national vaccination coverage cluster survey conducted between July 2019 and December 2019 by the NDoH. The survey adapted the methodology recommended in the WHO vaccination coverage cluster surveys reference manual. (WHO, 2018)

2.2. Study site

Data for this analysis were derived from the national vaccination coverage survey database. The survey covered all 52 districts in South Africa. However, in the present study we analyzed the survey data from three provinces, Eastern Cape, Gauteng and KwaZulu-Natal, since they possess a heterogeneous mix of urban and rural settings with varied demographics, hence results would be generalizable to the context of South Africa. Gauteng has 6 districts including the administrative capital of South Africa and is the

smallest but wealthiest of all the provinces in South Africa, and the most densely populated with the largest share of the country's population. KwaZulu-Natal has 10 districts and is the province with the second largest population. It lies along the subtropical east coast along the Indian Ocean, does share the boundary with Mozambique and is the most popular holiday destination in South Africa. Eastern Cape lies on the south-eastern coast and is one of the poorest provinces in South Africa and has 6 districts. (South African Government, 2021)

2.3. Study population – inclusion and exclusion criteria for the primary study

Eligible children in the primary study were aged 24 to 35 months at time of survey, and all mothers or care givers of eligible children in each household were interviewed. Instances where the household didn't participate in the survey, included the following; where the caregiver was present but refused to be interviewed and where no household member or no competent respondent was at home at time of visit or on repeat visit. Analysis of these data ensured that vaccine dropout rates of all the infant series of vaccines offered in EPI-SA could be calculated. The targeted cohort was eligible to receive the then most recent version of the national Road-to-Health card (RTHC) (NDoH, 2019) (WHO, 2018). Eligible children in this study were all children who met the criteria for inclusion in the primary study from Eastern Cape, Gauteng and KwaZulu-Natal Provinces.

2.4. Sample size

The study included data of all children included in the primary study from Eastern Cape, Gauteng and KwaZulu-Natal Provinces with documented date of birth which were captured in the survey dataset. Sample size calculation for the primary study were based on the formulae and rationale given in the WHO vaccination coverage cluster surveys reference manual (WHO, 2018). Based on parameters and assumptions set prior, the required sample size to estimate national vaccination coverage at 10% precision if expected full vaccination coverage is 65% = 14 351 children aged 24 to 35 months in 9204 clusters across all 52 districts in South Africa. In the survey, each district was a strata and clusters were small area layers (SALs). Clusters were randomly selected from a complete list of all strata (districts) that entirely covered the target population. As such, all the available data (sample size) from the selected study sites were sufficient to reliably meet the study aims.

2.5. Data Collection Process

To ensure privacy, no personal identifiers were included in the database for this analysis. Variables included demographic and vaccination data. Key variables included the following;

1. Child details
    a. Child's date of birth
    b. Child's age at time of survey
    c. Child's sex
2. Existence of a vaccination card
    a. If ever received
    b. If vaccination card was seen by fieldworker
    c. If that card is the one received when child was at first contact with the health system
    d. If the vaccination card is the standard given by NDoH
3. Vaccination details - data for the following vaccines were captured from the vaccination card or verbal recall: 1. BCG at birth, hexa1 at 6 weeks of age, hexa2 at 10 weeks of age, hexa3 at 14 weeks of age, MCV1 at 6 months and MCV2 at 12 months.
    a. If vaccine was administered
    b. Date when it was given, if recorded (for data captured from vaccination cards (RTHC))
    c. Reason(s) for missing a dose, if a vaccine was missed

2.6. Data management and analysis

The data underwent quality checks and a cleaning procedure, that included checking for missing data and duplications followed by analysis using Stata 15 ® (StataCorp (2017) Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC). Microsoft Excel was used to generate the figures. The continuous variable (age) was not normally distributed, hence the descriptive statistics were presented as median [interquartile range (IQR)]. Categorical data were presented as frequencies and percentages. Both chi-squared and Fisher's exact tests (for small cell counts) were used to test if there were statistically significant differences in vaccination timing following the recommended schedule across the three provinces for each vaccination schedule. The Mann–Whitney test and the Kruskal–Wallis H test were used to test differences between variables that were not normally distributed. Statistical significance was set at a two-tailed P-value of <= 0.05.

Only children whose data were collected from the RTHC were included in vaccination timeliness analysis as they showed complete and documented dates of birth and vaccine dose administration (day, month and year) compared to those whose data were collected from verbal recall as dates would likely not be accurate. Timeliness for each individual vaccine dose was categorized as follows; (1) Early - before EPI recommended date, (2) Timely - within 28 days following the recommended date, (3) Delayed – 28 days or more after the recommended date and (4) unvaccinated/missed doses – no evidence to have received a vaccine. Timeliness was calculated for each dose received by the child in reference to their date of birth. We defined timeliness age range for timely vaccination for each vaccine as vaccination within 28 days following the recommended age for vaccine administration in the EPI schedule. We defined dropout rate as the proportion of children who got an earlier vaccine dose, but didn't get the later dose. Dropout rate was measured for hexa1-hexa3, MCV1-MCV2 and BCG-MCV2, and analyses included data from RTHC and verbal recall as there was overlap of data source in some individuals, especially those who lost an initial RTHC where earlier vaccines were documented and got a new RTHC that only had later vaccines and vice-versa. The median age at vaccination for each vaccine dose among those delayed and those not delayed was calculated as the number of days after birth at which 50% of children had been vaccinated. For easy representation of the data in the table, weeks for the recommended age at vaccination were converted to months; as 6 weeks to 1.5 months, 10 weeks to 2.5 months, and 14 weeks to 3.5 months.

2.7. Ethics

Ethical and scientific approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) prior to initiation of the study with an ethical clearance certificate number M210629. The study protocol was reviewed and approved by the University of the Witwatersrand School of Pathology postgraduate assessors committee. The study only involved existing anonymized survey data. The study had no more than minimal risk to the subjects. The data were de-identified and anonymized, with the dataset stored electronically in a password protected computer with access only to the investigators.

2.8. Funding

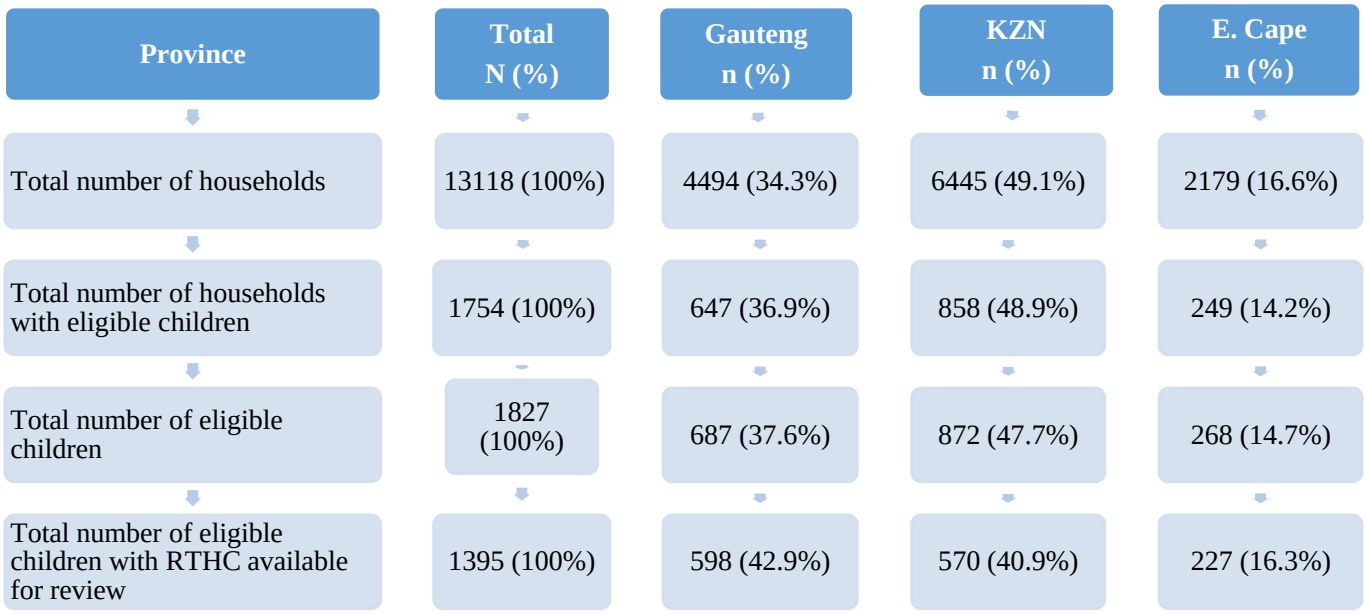
This research project was self-funded. Notable expenses included the purchase of the computer and data storage device, travel and communication expenses, printing and binding of the protocol and research report.

3. RESULTS

3.1. Demographic characteristics of children, 3 provinces, Republic of South Africa (RSA), 2019

Of the 1,827 children included in the analysis, 872 (47.7%) came from KwaZulu-Natal with Eastern Cape contributing the least, 268 (14.7%). (Figure 3.1 and Table 3.1) Overall, sex was equally distributed among the children included in the analysis, with 921 (50.4%) males and 906 (49.6%) females. A similar sex distribution was noted in each of the three provinces (Table 3.1). The overall median age at time of survey was 29 months (IQR: 26-32), and no age differences were noted between the provinces. (Table 3.1) Overall, the most number of households visited and most number of households with eligible children were in KwaZulu-Natal (6445 and 858) followed by Gauteng (4494 and 647) then Eastern Cape (2179 and 249). (Figure 3.1)

Figure 3.1: Flow diagram of eligible households and children , by province



Abbreviations: E.Cape, Eastern Cape; KZN, KwaZulu-Natal; RTHC, Road to Health Card.

Table 3.1: Distribution of children by age, sex and province, 3 provinces, RSA, 2019

Province	Total N (%)	Total: median age months (IQR)	Males n (%)	Males: median age months (IQR)	Females n (%)	Females : Median age months (IQR)
Gauteng	687 (37.6)	29 (26-32)	340 (49.5)	29 (26-32)	347 (50.5)	29 (26-32)
KZN	872 (47.7)	29 (26-32)	445 (51.0)	29 (26-32)	427 (49.0)	29 (26-32)
E. Cape	268 (14.7)	29 (27-32)	136 (50.8)	29 (27-32)	132 (49.3)	29 (26-33)
Overall Total	1,827 (100)	29 (26-32)	921 (50.4)	29 (26-32)	906 (49.6)	29 (26-32)

Abbreviations: E.Cape, Eastern Cape; KZN, KwaZulu-Natal.

3.2. Timeliness of vaccine antigens administered to children

Data for the following number of children were included in the timeliness analysis; 1,395 for BCG vaccine, 1,352 for hexa1 vaccine, 1,352 for hexa2 vaccine, 1,336 for hexa3 vaccine, 1,398 for MCV1 vaccine and 1,398 for MCV2 vaccine. (Table 3.2).

3.2.1. Overall vaccination timeliness and age at vaccine administration

Table 3.2 presents the distribution of vaccine dose timeliness per province. Of the children included in the timeliness analysis, children having a delayed administration by ≥28days was 80 (5.7%) for BCG dose; 120 (8.9%), 171 (12.7%) and 234 (17.5%) for the first, second and third dose of hexa; and, 312 (22.3%) and 350 (25.0%) for MCV1 and MCV2 respectively. (Table 3.2) The percentage of missed doses by the second birthday was lowest for BCG, at 19 (1.4%) and highest for MCV2, at 150 (10.7%), that is, when comparing all the vaccine antigens in the analysis. (Table 3.2) Overall, the proportion of children who received the next dose of whichever vaccine on time decreased while those receiving a delayed dose of whichever vaccine increased with each subsequent dose in the schedule. (Figure 3.2)

3.2.2. Timeliness and median delay period of BCG vaccination

The overall coverage among children who received timely vaccination, delayed vaccination or no vaccination for BCG was 92.9%, 5.7% and 1.4% respectively. (Table 3.2) The median age at BCG vaccination among those delayed was 2.2 (IQR: 1.4-6.1) months. (Table 3.3) In terms of BCG vaccination status across the three provinces studied, Gauteng had the highest proportion of children vaccinated, with majority having been vaccinated on time (95.3%), while KwaZulu-Natal had the least proportion of children vaccinated on time (90.2%) and also the highest proportion of children who had not received BCG by the second birthday (2.3%). (Figure 3.3)

3.2.3. Timeliness, and median delay period of hexa1, 2 and 3 vaccine doses

The overall coverage for early vaccination, timely vaccination, delayed vaccination and those who missed hexa1 was 13.1%, 74.7%, 8.9% and 3.3% respectively, for hexa2 was 12.0%, 70.7%, 12.7% and 4.7% respectively and for hexa3 was 10.9%, 66.5%, 17.5% and 5.1% respectively. (Table 3.2) The median age at vaccination among those delayed was 3.1 (IQR: 2.6-5.1), 4.0 (IQR: 3.5-5.5) and 5.3 (IQR:

4.5-8.1) months for hexa1, 2 and 3 respectively. (Table 3.3) Figure 3.4 presents the proportion of children by hexa1, 2 and 3 vaccination status across provinces.

Overall, the proportion of children receiving delayed doses increased with each subsequent dose, with the highest proportion of delayed doses noted in hexa3 (17.5%) and highest proportion of doses of hexa1 given on time (74.1%). Gauteng had the highest proportion of doses given on time for all three hexa doses (78.0%, 76.2% and 73.8%) followed by KwaZulu-Natal (73.9%, 66.5% and 63.9%), then Eastern Cape (67.8%, 66.2% and 54.2%). (Figure 3.4)

3.2.4. Timeliness and median delay period of MCV 1 and 2 vaccine doses

The overall coverage for early vaccination, timely vaccination, delayed vaccination and those who missed doses for MCV1 was 8.2%, 64.5%, 22.3% and 4.9% respectively while for MCV2 was 8.8%, 55.4%, 25.0% and 10.7% respectively. (Table 3.2) The median age in months at vaccination among those delayed was 8.6(IQR: 7.4-11.0) for MCV1 and 15.1(IQR: 13.6-19.0) for MCV2 vaccination. (Table 3.3)

Figure 3.5 presents the proportion of children by MCV1 and 2 vaccination status across provinces. Overall, a higher proportion of children received MCV1 vaccine on-time compared to MCV2 (64.5% vs 55.4%). As with the earlier vaccine doses, the highest proportion of children receiving MCV1 and MCV2 doses on time lived in Gauteng (72.7% and 64.8%). However, KwaZulu-Natal had the lowest proportion of children receiving the MCV1 dose (59.6%) and Eastern Cape had the lowest proportion of children receiving MCV2 dose (46.3%). (Figure 3.5)

3.2.5. Age at vaccination for children with delayed vaccination

For those with delayed vaccination, the median age at vaccination among those for BCG, hexa1, 2 and 3, and MCV1 and 2 was 2.2(IQR1.4-6.1), 3.1(IQR 2.6-5.1), 4.0(IQR 3.5-5.5), 5.3(IQR 4.5-8.1), 8.6(IQR 7.4-11.0) and 15.1(IQR 13.6-19.0) months respectively. (Table 3.3)

Table 3.2: Distribution of vaccination timeliness following National EPI schedule, 3 provinces, RSA, 2019

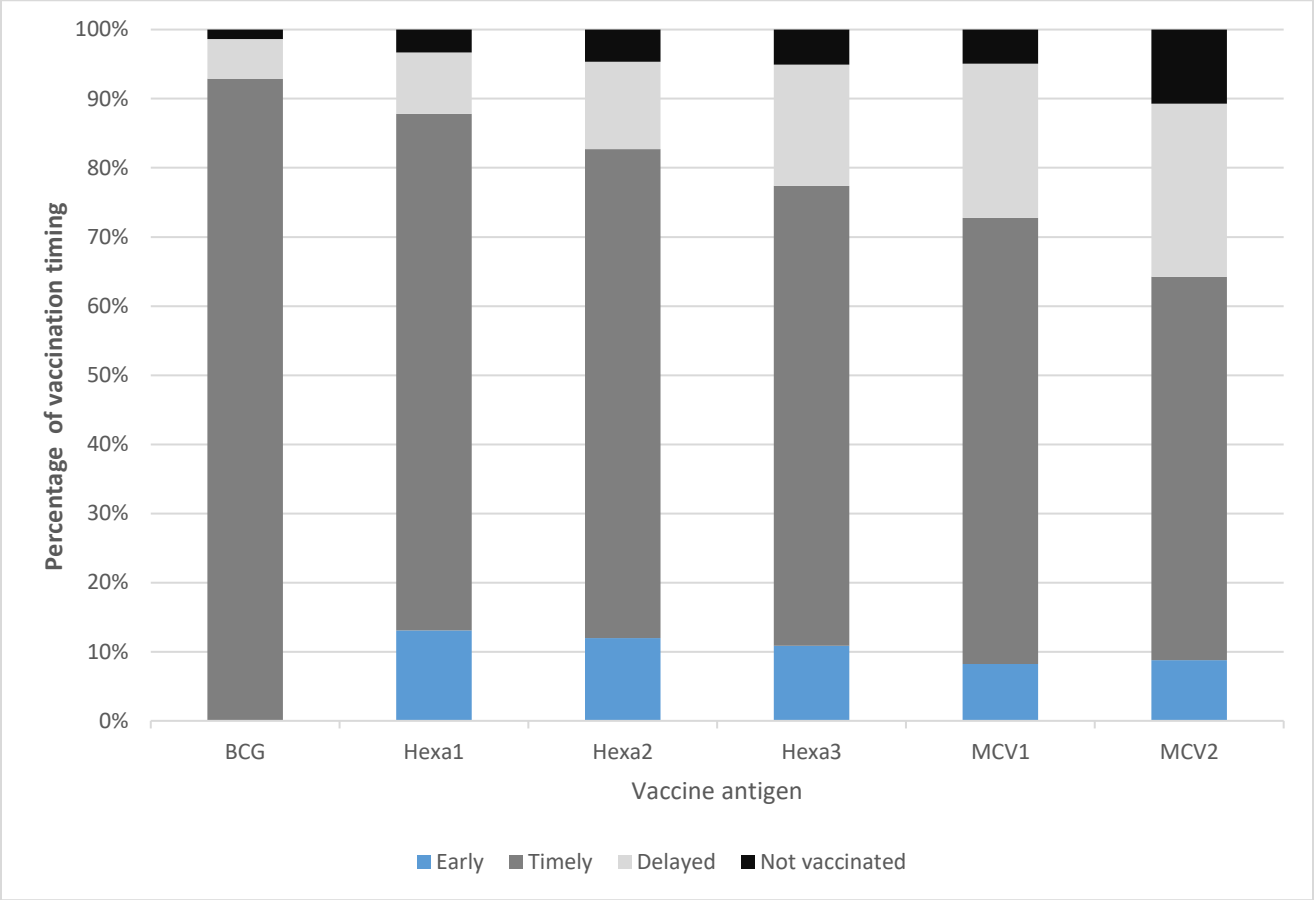
Vaccine Antigen	Province	N (column %)	Frequency of vaccination timing following the recommended schedule (n, (%))				
			Early - Before EPI recommended schedule	Timely - Within a month following recommended schedule	Delayed - A month or more after recommended schedule	Missed doses - not received a vaccine by the second birthday	Chi-square or Fisher exact P-value
BCG	E. Cape	227 (16.3)	N/A	212 (93.4)	13 (5.7)	2 (0.9)	
	Gauteng	598 (42.9)	N/A	570 (95.3)	24 (4.0)	4 (0.7)	
	KZN	570 (40.9)	N/A	514 (90.2)	43 (7.5)	13 (2.3)	
	Total	1395 (100)	N/A	1,296 (93.0)	80 (5.7)	19 (1.4)	0.011
Hexavalent (DTaP-IPV-HiB-HBV)1	E. Cape	227 (16.8)	35 (15.4)	154 (67.8)	29 (12.8)	9 (4.0)	
	Gauteng	596 (44.1)	75 (12.6)	465 (78.0)	47 (7.9)	9 (1.5)	
	KZN	529 (39.13)	67 (12.7)	391 (73.9)	44 (8.3)	27 (5.1)	
	Total	1352 (100)	177 (13.1)	1,010 (74.7)	120 (8.9)	45 (3.3)	0.004
Hexavalent (DTaP-IPV-HiB-HBV)2	E. Cape	228 (16.9)	30 (13.2)	151 (66.2)	37 (16.2)	18 (4.4)	
	Gauteng	596 (44.1)	60 (10.1)	454 (76.2)	64 (10.7)	18 (3.0)	
	KZN	529	72 (13.6)	351 (66.5)	70 (13.3)	35 (6.6)	0.003

		(39.1)					
	Total	1,352 (100)	162 (12.0)	956 (70.7)	171 (12.7)	63 (4.7)	
Hexavalent (DTaP-IPV-HiB-HBV)3	E. Cape	225 (16.8)	27 (12.1)	122 (54.2)	62 (27.6)	14 (6.2)	
	Gauteng	576 (43.1)	52 (9.0)	425 (73.8)	78 (13.5)	21 (3.7)	
	KZN	535 (40.0)	66 (12.3)	342 (63.9)	94 (17.6)	33 (6.2)	
	Total	1,336 (100)	145 (10.9)	889 (66.5)	234 (17.5)	68 (5.1)	<0.0001
MCV 1	E. Cape	226 (16.2)	31 (13.7)	126 (55.8)	58 (25.7)	11 (4.9)	
	Gauteng	596 (42.6)	37 (6.2)	433 (72.7)	103 (17.3)	23 (3.9)	
	KZN	576 (41.2	47 (8.2)	343 (59.6)	151 (26.2)	35 (6.1)	
	Total	1,398 (100)	115 (8.2)	902 (64.5)	312 (22.3)	69 (4.9)	<0.0001
MCV 2	E. Cape	229 (16.4)	32 (14.0)	106 (46.3)	58 (25.3)	33 (14.4)	
	Gauteng	594 (42.5)	43 (7.2)	385 (64.8)	110 (18.5)	56 (9.4)	
	KZN	575 (41.1)	48 (8.4)	284 (49.4)	182 (31.7)	61 (10.6)	
	Total	1,398 (100)	123 (8.8)	775 (55.4)	350 (25.0)	150 (10.7)	<0.0001

Fisher exact used where the cells <5

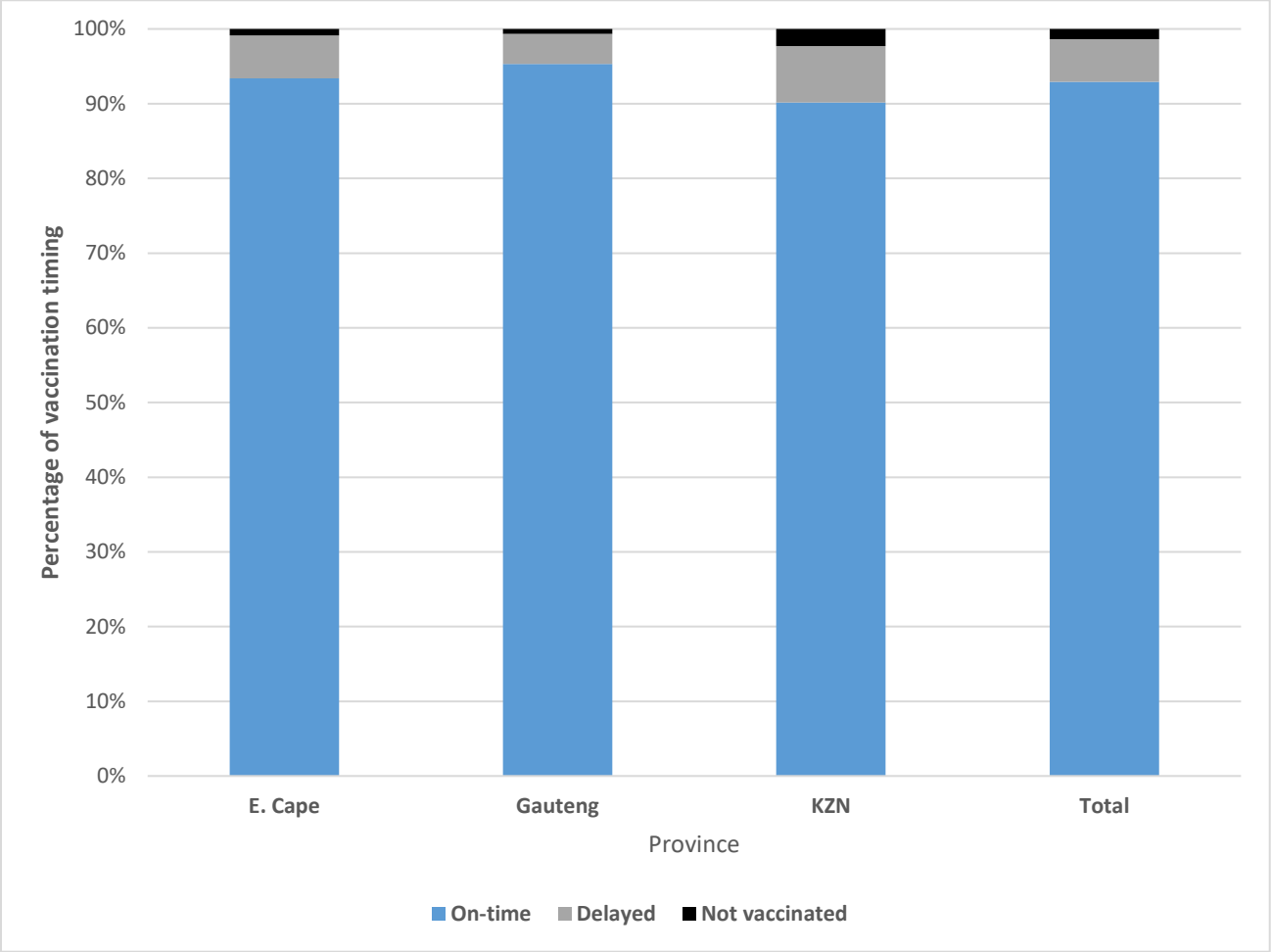
Abbreviations: BCG, Bacille Calmette-Guérin; E.Cape, Eastern Cape; KZN, KwaZulu-Natal; MCV, measles containing vaccine. Vaccination delay is defined as occurring 28days or more beyond the upper limit of the recommended vaccination administration range.

Figure 3.2: Percentage of children by vaccination status across the vaccination milestone visits, 3 provinces, RSA, 2019



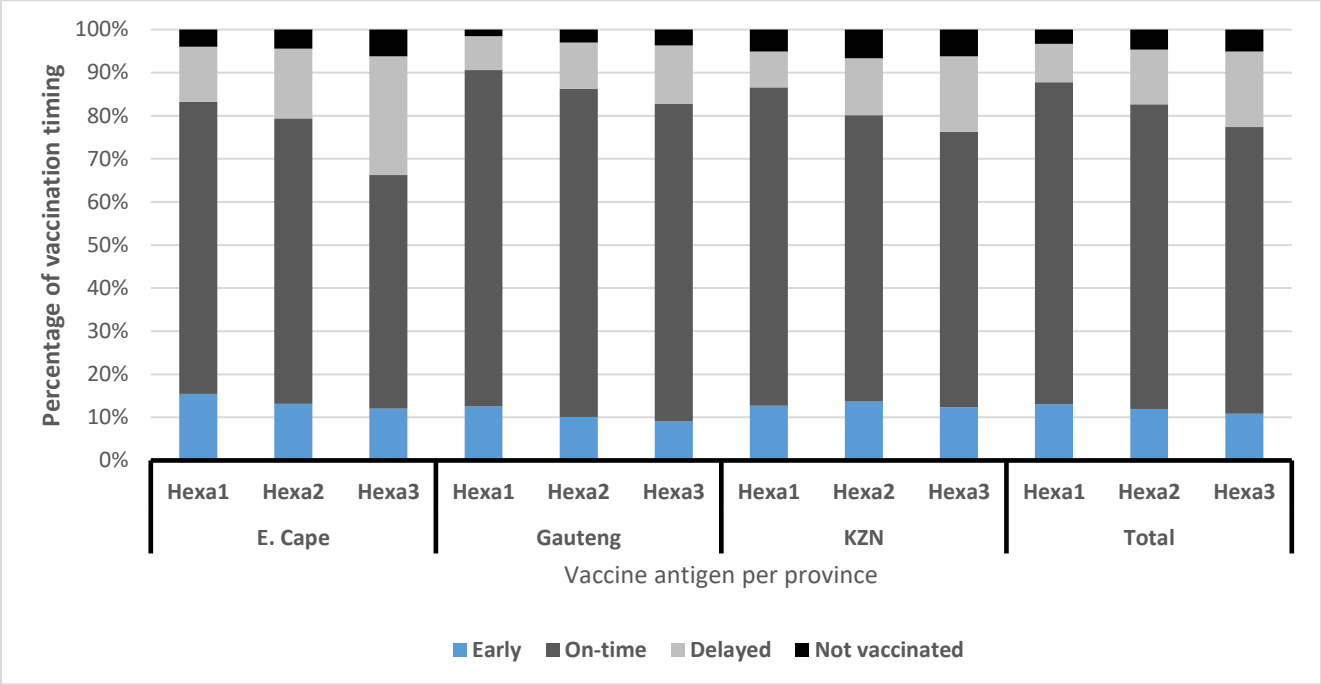
Abbreviations: BCG, Bacille Calmette-Guérin; Hexa: hexavalent containing vaccine; MCV, measles containing vaccine

Figure 3.3: Percentage of children by BCG vaccination status across provinces, 3 provinces, RSA, 2019



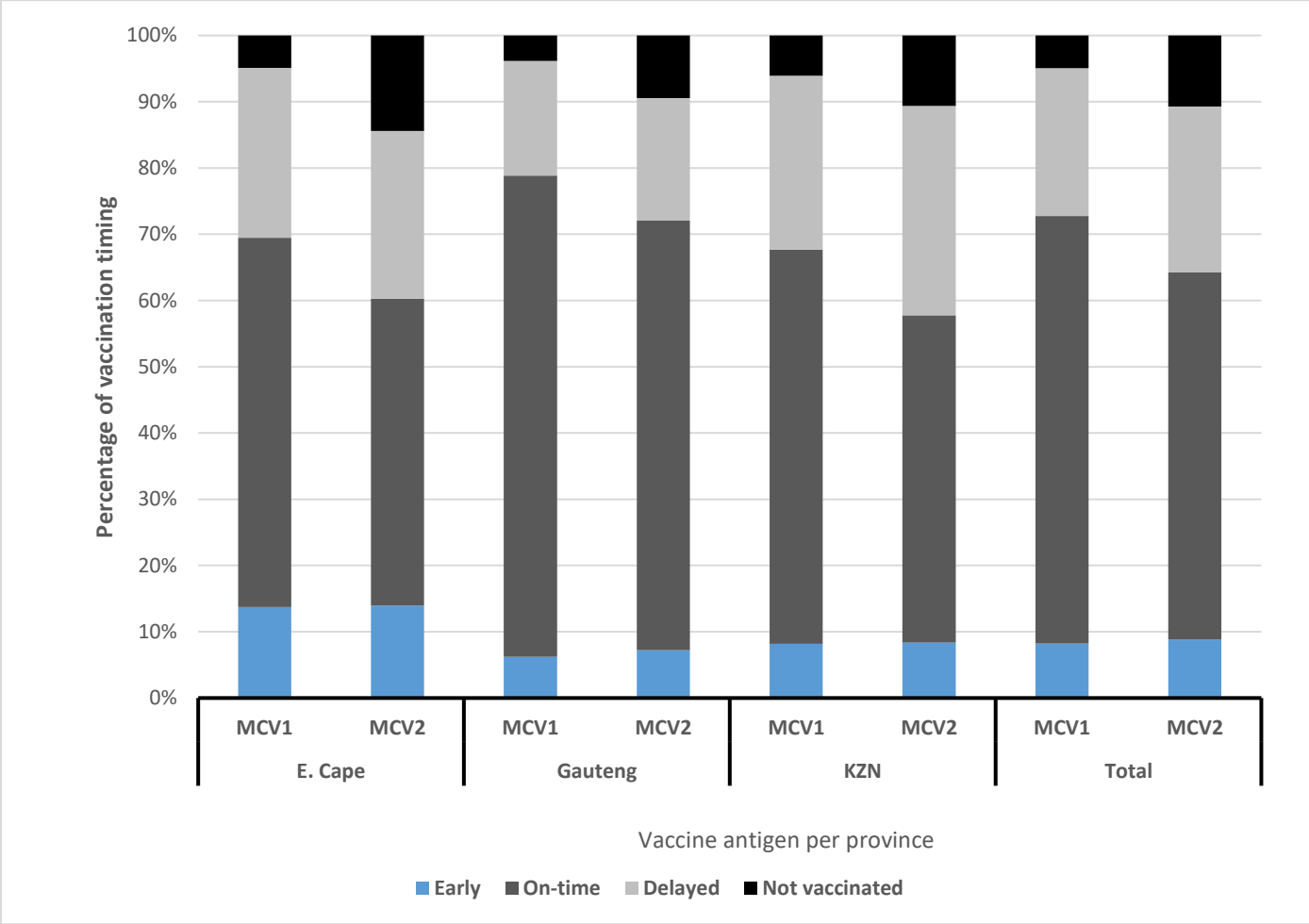
Abbreviations: BCG, Bacille Calmette-Guérin; E.Cape, Eastern Cape; KZN, KwaZulu-Natal. Vaccination delay is defined as occurring 28days or more beyond the upper limit of the recommended vaccination administration range.

Figure 3.4: Percentage of children by hexa1, 2 and 3 vaccination status across provinces, 3 provinces, RSA, 2019



Abbreviations: Hexa, hexavalent containing vaccine; E.Cape, Eastern Cape; KZN, KwaZulu-Natal. Vaccination delay is defined as occurring 28 days or more beyond the upper limit of the recommended vaccination administration range.

Figure 3.5: Percentage of children by MCV1 and 2 vaccination status across provinces, 3 provinces, RSA, 2019



Abbreviations: E.Cape, Eastern Cape; KZN, KwaZulu-Natal; MCV, measles containing vaccine. Vaccination delay is defined as occurring 28days or more beyond the upper limit of the recommended vaccination administration range.

Table 3.3: Age at vaccine administration, 3 provinces, RSA, 2019

Vaccine	Province	Timeliness range (months)	Median age in months among those vaccinated on-time (IQR)	Median age in months at vaccination among those delayed (IQR)	Probability dose delayed or not given
BCG	E. Cape	0-28days	0.03(0-0.07)	2.0(1.1-4.7)	7%
	Gauteng		0.03(0-0.07)	2.0(1.4-6.1)	5%
	KZN		0.03(0-0.03)	2.5(1.5-7.6)	10%
	Total		0.03(0-0.03)	2.2(1.4-6.1)	7%
Hexa1	E. Cape	6week-10weeks	1.5(1.4-1.6)	2.7(2.5-3.8)	17%
	Gauteng		1.5(1.4-1.6)	3.0(2.6-4.6)	9%
	KZN		1.5(1.4-1.6)	3.6(2.6-6.3)	13%
	Total		1.5(1.4-1.6)	3.1(2.6-5.1)	13%
Hexa2	E. Cape	10weeks-14weeks	2.5(2.4-2.7)	3.9(3.6-4.7)	21%
	Gauteng		2.5(2.4-2.6)	3.9(3.5-5.5)	14%
	KZN		2.5(2.4-2.6)	4.1(3.7-6.0)	20%
	Total		2.5(2.4-2.7)	4.0(3.5-5.5)	18%
Hexa3	E. Cape	14weeks-18weeks	3.5(3.3-3.7)	4.8(4.4-7.5)	34%
	Gauteng		3.5(3.3-3.7)	5.0(4.5-7.2)	17%
	KZN		3.5(3.3-3.7)	6.0(4.6-8.4)	24%
	Total		3.5(3.3-3.7)	5.3(4.5-8.1)	25%
MCV1	E. Cape	6-7 completed months	6.2(6.1-6.4)	8.5(7.3-11.2)	31%
	Gauteng		6.2(6.1-6.3)	8.5(7.3-10.0)	21%
	KZN		6.3(6.1-6.5)	8.7(7.5-11.4)	32%
	Total		6.2(6.1-6.4)	8.6(7.4-11.0)	28%
MCV2	E. Cape	12-13 completed months	12.3(12.2-12.5)	15.5(13.0-20.3)	40%
	Gauteng		12.3(12.2-12.4)	14.7(13.4-18.4)	28%
	KZN		12.2(12.2-12.5)	15.2(13.7-18.9)	42%

	Total		12.3(12.2-12.5)	15.1(13.6-19.0)	37%

Abbreviations: BCG, Bacille Calmette-Guérin; MCV, measles containing vaccine; IQR, interquartile range (between 25th and 75th percentile); E.Cape, Eastern Cape; KZN, KwaZulu-Natal.

3.3. Vaccination dropout rates among children

Overall, we observed that the dropout rate from hexa1 to hexa 3 was 2.1% while that for MCV1-MCV2 was 5.3%. (Table 3.4 and Table 3.5) The highest dropout rates for hexa1-hexa3 was in Eastern Cape (3.9%) followed by Gauteng (1.9%) and then KwaZulu-Natal (1.8%). As with hexa1-hexa3, the highest dropout rates for MCV1-MCV2 was in Eastern Cape (9.3%) followed by Gauteng (5.4%) and then KwaZulu-Natal (3.9%). The overall general dropout (BCG-MCV2) rate was 8.1%, with the highest rate noted in Eastern Cape (12.5%) followed by Gauteng (8.0%) then KwaZulu-Natal 6.8%. (Table 3.6)

Table 3.4: hexa1–hexa3 vaccination dropout rate, 3 provinces, RSA, 2019

Vaccine Dose	Source of data	Province			
		E. Cape	Gauteng	KZN	Total
Children who received hexa1 dose	Card-verified n(%)	218 (16.7%)	587 (44.9%)	502 (38.4%)	1307 (100%)
	Verbal recall n(%)	41 (8.6%)	91 (19.2%)	343 (72.2%)	475 (100%)
	Card+ verbal recall N(%)	259 (14.5%)	678 (38%)	845 (47.4%)	1782 (100%)
Children who received hexa3 dose	Card-verified n(%)	1782 (100%)	554 (44.2%)	493 (39.3%)	1254 (100%)
	Verbal recall n(%)	42 (8.6%)	111 (22.7%)	337 (68.8%)	490 (100%)
	Card+ verbal recall N(%)	249 (14.3%)	665 (38.1%)	830 (47.6%)	1744 (100%)
Specific dropout rate (%): (1-Proportion of children vaccinated with hexa3 among those that received hexa1)	Card+ verbal recall N(%)	3.9%	1.9%	1.8%	2.1%

Abbreviations: E.Cape, Eastern Cape; KZN, KwaZulu-Natal; hexa, hexavalent containing vaccine

Table 3.5: MCV1-MCV2 vaccination dropout rate, 3 provinces, RSA, 2019

Vaccine Dose	Source of data	Province			
		E. Cape	Gauteng	KZN	Total
Children who received hexa1 dose	Card-verified n(%)	215 (16.2%)	573 (43.1%)	541 (40.7%)	1329 (100%)
	Verbal recall n(%)	42 (9.8%)	91 (21.2%)	296 (69.0%)	429 (100%)
	Card+ verbal recall N(%)	257 (14.6%)	664 (37.8%)	837 (47.6%)	1758 (100%)
Children who received hexa3 dose	Card-verified n(%)	194 (15.7%)	535 (43.2%)	509 (41.1%)	1238 (100%)
	Verbal recall n(%)	39 (9.1%)	93 (21.8%)	295 (69.1%)	427 (100%)
	Card+ verbal recall N(%)	233 (14.0%)	628 (37.7%)	804 (48.3%)	1665 (100%)
Specific dropout rate (%): (1-Proportion of children vaccinated with hexa3 among those that received hexa1)	Card+ verbal recall N(%)	9.3%	5.4%	3.9%	5.3%

Abbreviations: E.Cape, Eastern Cape; KZN, KwaZulu-Natal; MCV, measles containing vaccine.

Table 3.6: Overall BCG-MCV2 vaccination dropout rate, 3 provinces, RSA, 2019

Vaccine Dose	Source of data	Province			
		E. Cape	**Gauteng**	**KZN**	**Total**
Children who received hexa1 dose	Card-verified n(%)	225 (16.4%)	594 (43.2%)	557 (40.5%)	1376 (100%)
	Verbal recall n(%)	40 (11.5%)	80 (23.1%)	227 (65.4%)	347 (100%)
	Card+ verbal recall N(%)	265 (15.4 %)	674 (39.1%)	784 (45.5%)	1723 (100%)
Children who received hexa3 dose	Card-verified n(%)	194 (15.9%)	530 (43.4%)	498 (40.8%)	1222 (100%)
	Verbal recall n(%)	38 (10.5%)	90 (24.9%)	233 (64.5%)	361 (100%)
	Card+ verbal recall N(%)	232 (14.7%)	620 (39.2%)	731 (46.2%)	1583 (100%)
Specific dropout rate (%): (1-Proportion of children vaccinated with hexa3 among those that received hexa1)	Card+ verbal recall N(%)	12.5%	8.0%	6.8%	8.1%

Abbreviations: BCG, Bacille Calmette-Guérin; E.Cape, Eastern Cape; KZN, KwaZulu-Natal; MCV, measles containing vaccine.

3.4. Reasons given for missing a vaccine dose

Table 3.7 presents the reasons reported by 308 caregivers why their children missed vaccine doses for any of BCG, hexa1-3 and MCV1-2. Of 308 documented reasons for missing a vaccine dose, 73 (23.7%) caregivers reported that their child had reached the health facility but could not be vaccinated due to the health facility being closed, no vaccinator available or vaccine stock-outs. Indeed, among those 73 caregivers, 67 (91.8%) reported that vaccine was out-of-stock at the health facility. A further 59 (19.2%) of the 308 reasons reported for missed doses were due to the unavailability of the caregiver due to work or illness. The reasons given for missing a vaccine dose were not different per province.

Table 3.7: Reasons given for missing a vaccine dose, 3 provinces, RSA, 2019.

Reason why vaccine dose was not given		**n (%)**	**N (%)**
Lack of knowledge	Primary caregiver didn't know that child must be vaccinated	36 (11.7%)	48 (15.6%)
	Primary care giver forgot that child had to be vaccinated	12 (3.9%)	
Physical barrier	Health facility is too far (distance)	26 (8.4%)	26 (8.4%)
Hesitancy	Parents refused the vaccine	1 (0.3%)	9 (2.9%)
	Religious reasons	8 (2.6%)	
Child's health related reasons	Child was ill and not taken to health	8 (2.6%)	13 (4.2%)
	Child was ill and taken to health facility but was not given vaccine	5 (1.6%)	
No one to take child for vaccination	There was no one to take the child for vaccination	24 (7.8%)	59 (19.2 %)
	Primary care giver was sick	18 (5.8%)	
	Primary caregiver was at work	17 (5.5%)	
Health facility related factors	Went to health facility and found them closed	0 (0.0%)	73 (23.7%)
	Went to health facility and was told vaccinator was not available	6 (2.0%)	
	Vaccine was out of stock	67 (21.8%)	
Others		80 (26.0%)	80 (26%)
			308 (100%)

4. DISCUSSION

Using data for three selected provinces from the South African national vaccination coverage survey conducted in 2019, the present study measured vaccination timeliness, dropout rates and, the major reasons reported for missing vaccine doses. The study showed that the proportion of children who missed a vaccine dose in the national EPI schedule increased with subsequent vaccine antigens, being 1.4%, 3.3%, 4.7%, 5.1%, 4.9% and 10.7% for BCG, hexa1, hexa2, hexa3, MCV1 and MCV2, respectively. The timeliness of vaccine adminstration for each vaccine dose were dissappointing, with 5.7%, 8.9%, 12.7%, 17.5%, 22.3%, and 25.0% accessing vaccinations for BCG, hexa1, hexa2, hexa3, MCV1 and MCV2 respecively over one month late. The dropout rates for hexa1, a vaccine given at 6 weeks, to hexa3, a vaccine given at 14 weeks, was relatively low at 2.1% while that for MCV1, a vaccine given at 6 weeks, to MCV2, a vaccine given at 12 months, was high at 5.3%. However, 8.1% of children who received BCG vaccine failed to complete their vaccination schedule with MCV2.

Of 308 documented reasons for missing a vaccine dose, 73 (23.7%) of the reported 308 caregivers reported that their child had reached the health facility but could not be vaccinated due to the health facility being closed, no vaccinator available or vaccine stock-outs. Indeed, among those 73 caregivers, 67 (91.8%) reported that vaccine was out-of-stock at the health facility. A further 59 (19.2%) of the 308 reasons reported for missed doses were due to the unavailability of the caregiver due to work or illness. This study further revealed substantial provincial differences with Gauteng performing well across most indicators.

4.1. Timeliness and dropout

Ensuring that children have access to scheduled vaccine doses on time has proved to be a critically important and cost-effective model to decrease the incidence of disease and related morbidity within a population. Assessment of vaccination timeliness is thus an important indicator for monitoring immunization program and hence it serves as an essential element in the evaluation and targeted improvement of immunization performance. In the present study, the probability of receiving a vaccine dose outside the recommended period increased from 7% (5.7% delayed, 1.3% missed) for BCG, a vaccine administered at birth, to 44.5% (8.8% early, 25.0% delayed, 10.7% missed) for MCV2, a vaccine at scheduled at 12 months.

We observed a high proportion of vaccine doses administered early, before the recommended age, as follows; 13.1% for hexa1, 12% for hex2, 10.9% for hexa3, 8.2% for MCV1 and 8.8% for MCV2. Such early doses can be a big concern, as may lead to immunity blunting effect hence not to confer full or adequate long-term immunity to children resulting in lower antibody titres even in the follow up doses, unlike when given later or at the recommended age. (Lochlainn, et al., 2019) This has been well studied with MCV1, where the optimal timing for administration has varied across different settings and MCV vaccine effectiveness has noted to decrease with younger age at administration. (Carazo, et al., 2020) (Xu, et al., 2021)

It can be difficult to make comparisons with other studies as there may be important differences in the definition of vaccine timeliness and delay in the published data, with studies using categorical or continuous measures of timeliness. (Masters, et al., 2019) However, results in our study showed relatively fewer late doses compared to data from several countries in the African region. A study that pooled data from 33 Sub-Saharan African countries revealed higher dose-specific delays when compared to our study, with proportion of children with a delayed vaccination of more than month as follows: 25.9% for BCG vaccine, 49.1% for the pentavalent 3 vaccine (similar to hexavalent 3) and 63.9% for the first dose of measles containing vaccines. (Janusz, et al., 2020) An earlier study in South Africa reported higher proportions of vaccination timeliness when compared to our study, with 99% for BCG, 87% for DPT1, 90% for DPT2 and 85% for DPT3. (Fadnes, et al., 2011) However, this study used a wide vaccination timeliness age range (birth – 8 weeks for BCG at birth, 4 weeks to 2 months for DPT1 at 6 weeks, 8 weeks – 4 months for DPT2 at 10 weeks and 10 weeks – 6 months for DPT3 at 14 weeks) compared to our study where timeliness age range for timely vaccination for each vaccine was defined as vaccination within 28 days following the recommended age. Our study also showed better timeliness than recently published data from West Africa where the proportion of children with delayed vaccintion rose from 23.3% for BCG vaccine to 31.7% for MCV1 in the year 2018. (Ateudjieu, et al., 2020)

Similar to other studies, we assessed timeliness of BCG, hexa and measles containing vaccines as are related to protect from diseases of concern at international level. It is noted from the study that the overall proportion of children who received a delayed dose and or who missed a dose increased from one vaccination contact to the next, with MCV3 followed by MCV2 and then MCV1 having a progressively higher probability of dose delayed or missed. Such findings are of a big concern considering measles is

a disease intended for global eradication. (Patel, et al., 2020) These findings illustrate the fragility of progress towards global eradication plans considering that the disease is highly contagious, and that timely vaccination is critical to reduce the number of susceptible individuals. (Gay, 2004)

Hexavalent containing vaccine protects against several serious infections including; diphtheria, tetanus, pertussis, polio, Hib and HepB. The high proportion of receiving a hexa3 dose late or not at all is of considerable concern as it also reflects the ability to retaining a child in a vaccination program on multiple visits. It is also for the same reasons why DPT3, penta3 or hexa3 vaccination coverage is a key indicator of immunization program performance globally. (Brown, et al., 2011) In our study, 66.5% of the children received a hexa3 dose on-time. However, similar analysis done in Vietnam, India and Colombia found that 45%, 35% and 49% of DPT3 vaccine was administered on time respectively which are relatively lower levels of timeliness when compared to our study. (Wagner, et al., 2018) (Narváez, et al., 2017) (An, et al., 2016) Similar vaccination timeliness results were also reported from studies done in several different settings, including China and India. (Veerasingam, et al., 2017) (Hu, et al., 2017) (Shrivastwa, et al., 2016)

The results of this study indicate that, among children aged 24 to 35 months included in the study, the documented overall (BCG-MCV2) dropout rate was 8.1%, while the specific MCV1-MCV2 and hexa1-hexa3 dropout rates were 2.1% and 5.3% respectively. A similar analysis in West Africa revealed a general dropout rate and a DTP1-DTP3 containing vaccine specific dropout rate with evidence of 48% and 40.1% respectively among children of 12-23 months. (Ateudjieu, et al., 2020) However, this need to consider the fact that the West African study had participants with a lower age group, (12-23 months vs 24-35months), and that its vaccination schedule only had one dose of MCV, given at 9 months, compared to the South African schedule where two doses of MCV were given, at 6 and 12 months. Some published reports from high and LMICs showed a significant association of delayed vaccination as a risk of vaccination dropout. (Kiely, et al., 2018) (Emmanuel, et al., 2015) This was also noted in a recent study that analyzed data from 33 Sub-Saharan Africa countries where delayed vaccination was significantly associated with a high likelihood to not completing the vaccination schedule in the first year of life. (Janusz, et al., 2020)

4.2. Disparities at Provincial level and reasons for missing vaccine doses

Studies assessing the factors to vaccination delay and incomplete schedules revealed that such factors do vary based on development settings and contexts across different settings. (Veerasingam, et al., 2017) (Tauil, et al., 2016) This study had revealed significant provincial differences in vaccination timeliness, dropout rates and levels of doses missed. Gauteng, the wealthiest province in South Africa, with superior indicators at socio-economic levels compared to Eastern Cape which is categorized as one of the poorest province in South Africa, had the highest proportion of children vaccinated on time while a high proportion of doses delayed and those to have missed a vaccine dose was noted in Eastern Cape and KwaZulu-Natal. Again, Eastern Cape had the highest vaccination dropout rates as noted on completion of MCV1-MCV2, completion of hexa1- hexa3, and also most notably the general BCG-MCV2. These findings are consistent with most reports from elsewhere in Africa where a high proportion of delayed and missed doses was observed in settings with low levels of socio-economic and education, and high rates of home births. (Janusz, et al., 2020) (Bangura, et al., 2020) (Boulton, et al., 2019) The study found KwaZulu-Natal followed by Gauteng to have the highest proportion of children whose BCG dose was delayed. Such findings on BCG vaccination timeliness are consistent with findings from a review of recorded live bith data in 2018, that found KwaZulu-Natal (68,1%) followed by Gauteng (75,7%), to have the lowest percentage of birth registrations within 30 days compared to the rest of the provinces. (stats sa, 2019)

Such disparities at provincial level may not just reflect or expose variations in vaccine supply chain management, health-workforce and health facilities, but also reflect on a number of socio-demographic issues across the provinces that include levels of poverty, employment and literacy. Our study revealed the most frequently reported reasons for missing a vaccine dose indicated that the child never reached the health facility as there was no one to take the child for vaccination. However, overall, 21.8% of the documented reasons were specifically due to finding vaccine out of stock when the child had reached the health facility. Our findings are then consistent with those from previous studies in LMICs that also analyzed the reasons for vaccination delay, in which poor access to health services, poor immunization supply and family characteristics were the main determinant factors. (Rainey, et al., 2011) (Gram, et al., 2014) These issues are also reflected at provincial level in South Africa, hence the variations in vaccination timeliness and dropouts from the schedule.

4.3. Limitations

We acknowledge several limitations to the present study, which we hope will contribute a new perspective on vaccination timeliness, dropout rate and reasons for missed vaccination in South Africa. Only children whose data were collected from the RTHC were included in the vaccination timeliness analysis because we required that they have complete and documented date of birth and date of receiving each vaccine dose (day, month and year). This may have created a selection bias that may reduce the generalizability of our findings considering that those children who possessed a RTHC might not be fully representative of the general population. Such timeliness may be biased towards children who are likely to retain a RTHC. For example, in East Africa it was reported that a higher proportion (57.0%) of children with an immunization card were fully vaccinated unlike those without the card (11.2%). (Lakew, et al., 2015) However, we are satisfied that the 2019 RSA national vaccination coverage survey where only 24% (1395/1827) of eligible children included in our study did not have a vaccination card was well organized, questionnaires were pretested prior to the data collection, the data collection team were well oriented to the survey objectives and tools, and there was close supervision and data monitoring throughout the survey.

4.4. Recommendation

Based on the study findings, we would like to submit the following general recommendations: (1) The EPI-SA with support from NDoH and relevant stakeholders in immunization need to fully adopt the systematic use of the timeliness and dropout rate indicators at all levels in order to ensure that implemented interventions are tailored to address the major bottlenecks in immunization programs; (2) The EPI-SA must strongly discourage early vaccination doses throughout the course of the EPI schedule to ensure age-specific protection by use of continued emphasis on education for mothers/caregivers and providers by utilizing outreach campaigns and health facility visits; (3) The NDoH need to ensure health system strengthening activities at community and primary care level, that ensures well-equipped and organized vaccination centers/clinics, delivering health promotion and campaign messages through media houses, maternal and child health service integration at health facilities and reducing waiting times; (4) The EPI managers need to organise review meetings and trainings at all levels to plan and implement strategies that will ensure improved and sustained vaccine stock management; (5) The EPI managers at district and provincial level, and relevant stakeholders need to ensure they implement and

conduct review of the following strategies which have proved to perform in some settings; (a) use of SMS or phone calls for reminder and communication, (b) use of an electronic vaccination card with reminders, (c) education for caregivers and community outreach to improve demand for vaccination services, (d) strengthening regular vaccination checks at school and kindergarten and (e) to organise catch-up vaccination campaigns to reach out to all children beyond 2years with incomplete vaccination records. Most of these interventions have been well documented in recent studies. (Mekonnen, et al., 2021) (Nsubuga, et al., 2019) (Mekonnen, et al., 2019)

5. CONCLUSION

Using data from the South African national vaccination coverage survey conducted in 2019, the study found that vaccination timeliness and dropout rates were unable to meet the objective of EPI program. There was a trend towards increased levels of vaccination delay and incomplete schedules with the later vaccines administered later in the schedule, with increasing median age with each vaccination milestone among those receiving delayed vaccine. Also, most instances when a vaccine dose was missed, it was due to the fact that a child was never brought to the health facility and, in at least 1 in 5 instances, were due to finding vaccine out of stock when the child had reached the health facility. There are substantial provincial differences in vaccination timeliness, missed doses and incomplete schedules. The NDoH, EPI-SA and relevant stakeholders need to systematically use the timeliness and dropout rate indicators to ensure appropriate strategies that are tailored to address the major bottlenecks in immunization programs are implemented. Such interventions include catch-up vaccination campaigns to reach all children who missed a dose or dropped form the schedule and interventions to increase demand and timely uptake of the vaccines.

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7. APPENDICES

7.1. HREC (Medical) Clearance Certificate - M210629

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Ben Mabaleka Chavula

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M210629

NAME: (Principal Investigator)	Dr Ben Mabaleka Chavula
DEPARTMENT:	School of Pathology Vaccine and Infectious Diseases Analytics (VIDA) Research Unit
PROJECT TITLE:	Vaccination dropout in South Africa
DATE CONSIDERED:	25/06/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr P Mutevedzi, Dr C Cutland and Dr R Bielik
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/08/2021

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

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