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Impact of the COVID-19 pandemic on routine immunisation in Soweto and Thembelihle in Gauteng province, South Africa

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2022
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UNIVERSITY OF WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

SCHOOL OF PATHOLOGY

IMPACT OF THE COVID-19 PANDEMIC ON ROUTINE IMMUNISATION IN SOWETO AND THEMBELIHLE IN GAUTENG PROVINCE, SOUTH AFRICA.

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for Master of Science in Medicine in the
field of Vaccinology for the year 2022, Johannesburg 2022

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08/09/2022

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Declaration

I [Chikondi Charity Kandulu] declare that this research report is my own, unaided work. It is being submitted for the Degree [MSc Med in Vaccinology] at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



08th of September 2022

Abstract

Introduction

The Covid-19 pandemic had devastating direct and indirect effects across the world, including in South Africa. The pandemic placed immense pressure on the already burdened health care system coupled with the lockdown measures, which may have affected the timing of routine childhood immunisation services. This study aimed at assessing the impact of the COVID-19 pandemic on the timeliness of routine immunisation in South Africa.

Methods

We used data from the Soweto and Thembelihle HDSS South Africa collected between 2017 and 2021 to conduct a retrospective cohort analysis. Information on vaccination status was recorded from vaccination cards of children aged 0-23 months. We used Chi-square or Fisher's exact tests to compare the vaccination timeliness (early, timely, late), missed doses and reasons for missed doses between the pre-pandemic and pandemic periods of child routine vaccinations. We specifically included Bacillus Calmette-Guérin (BCG), 3 doses of the hexavalent vaccine (DTaP- HepB, IPV, Hib) (Hexaxim, hexa1, hexa3 and hexa4), 1 dose of the Pneumococcal Conjugate Vaccine (PCV3) and 1 dose of the Measles Conjugate Vaccine (MCV2)

Results

Of the 2888 eligible children, 1,427 children were born in the pre-pandemic period and 1461 in the pandemic period. The proportions of receiving BCG vaccine timely versus late during the pre-pandemic period compared to the pandemic period. were similar ($p=0.783$). However, the timeliness for receiving PCV3, hexa3, hexa4 and MCV2 vaccines were significantly different. between the pandemic and pre-pandemic periods at P-values of $p<0.001$, $p<0.001$, $p=0.013$ and $p<0.001$ respectively. Generally, early vaccines were received more in the pre-pandemic time than the pandemic time while more delayed in the pandemic than the pre-pandemic time. Finally, PCV3, hexa4 and MCV2 had better timeliness during the pandemic except for hexa3 which had better timeliness during the pre-pandemic period.

The proportions of missed doses between the two times were similar in all vaccines except MCV1 at a p value of 0.007. The primary caregiver was the main reason for missing rota2, PCV2 and PCV3 doses before the pandemic, while child illness for hexa3, rota2 and PCV2 during the pandemic

Conclusion

The COVID-19 pandemic was associated with delayed vaccination on some vaccines received later in childhood with child illness as the most common reason for missing vaccines during the pandemic, significantly manifesting its direct and indirect effects on routine immunisation and the health system. Policymakers and health system planners should ensure that catch-up programs are organised to avert vaccine-preventable diseases (VPDs).

Acknowledgements

I would like to thank and recognise the following people who made my research report possible. Dr Robin Biellik for his guidance, directions and support throughout the journey on both personal and academic accounts. Dr Portia Mutevedzi for her supervision from proposal writing and submission of the report. Dr Clare Cutland for the mentoring, guidance, support and understanding throughout the whole MSc journey. Professor Shabir Madhi for allowing me to conduct this analysis from his work. Mr Steven Aziz your encouragement, editing and statistics support was enormous. Dr Titus Divala for the continuous support, encouragement and reviewing of my work. Mrs Kandulu, my mom for moral support and prayers Mr Munyaradzi Mukoko for encouraging and providing Stata skills. Alane Izu for reviewing my proposal drafts Dr Nisha Makan for reviewing my proposal drafts Mrs Emily Kambalame for helping me with the ethics submission process. The staff of Chris Hani Baragwanath Academic Hospital, for allowing me to work with them and guiding me. Mr Andrew Makwinja for the continuous moral support. Without you, I would have given up at some point. And other people that are too numerous to mention.

Dedication

To God Almighty for his abundant mercies and guidance throughout my school. To my caregivers; Joel and Stella, and my siblings; Chimwemwe and Joel; all things are possible to those who work hard and believe and to my loving and understanding husband Andrew Kondaine Makwinja; thank you for your patience with me throughout the journey.

To my late aunt Gertrude Bvumbwe and her family for your prayers, encouragement and love in a foreign country. Your love kept me going.

Lastly, to myself for working tooth and nail and keeping ongoing despite a tough year and a year of loss that 2020 was.

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List of abbreviations and acronyms

AMR	Antimicrobial resistance
BCG	Bacille Calmette-Guérin
CHAMPS	Child Health and Mortality Prevention Surveillance system
COVID-19	Coronavirus disease 2019
DEC	December
DoH	Department of Health
DPT3	Third dose of DTP
EPI	Expanded Programme on Immunisation
EPI-SA	Expanded Programme on Immunisation of South Africa
GVAP	Global Vaccine Action Plan
HDSS	Health and Demographic Surveillance System
HCWs	Health Care Workers
Hexa1	First dose of Hexavalent vaccine containing Diphtheria-Pertussis-Tetanus-Inactivated Polio Haemophilus influenza type b –Hepatitis B vaccine
Hexa2	Second dose of Hexavalent vaccine containing Diphtheria-Pertussis-Tetanus-Inactivated Polio- Haemophilus influenzae type b – Hepatitis B vaccine
Hexa3	Third dose of Hexavalent vaccine containing Diphtheria-Pertussis-Tetanus-Inactivated Polio Vaccine- Haemophilus influenzae type b – Hepatitis B vaccine
Hexa4	Fourth dose of Hexavalent vaccine containing Diphtheria-Pertussis-Tetanus-Inactivated Polio Vaccine- Haemophilus influenzae type b – Hepatitis B vaccine
HICs	High Income Countries
HH	Household
HPV	Vaccine against human papillomavirus
Jan	January
IA2030	Immunisation agenda 2030
KZN	Kwa-Zulu Natal
LMCIs	Low- and middle-income countries
MCV1	First dose of the Measles Conjugate Vaccine
MCV2	Second dose of the Measles Conjugate Vaccine

MITS	Minimal Invasive Tissue Sampling
MUAC	Mid-Upper Arm Circumference
NAGI	National Advisory Group on Immunisation
OPV0	The first dose of the Oral Polio Vaccine
OPV1	Second dose of the Oral Polio Vaccine
PCV	Pneumococcal Conjugate Vaccine
PCV1	The first dose of the Pneumococcal Conjugate Vaccine
PCV2	Second dose of the Pneumococcal Conjugate Vaccine
PCV3	Third dose of the Pneumococcal Conjugate Vaccine
PGA	Postgraduate assessors
Rota1	The first dose of the rotavirus vaccine
Rota2	Second dose of rotavirus vaccine
RTHC	Road to Health Card
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SIAs	Supplementary Immunisation Activities
SBS	Social Behavioural Studies
SDG	Sustainable Development Goal
SES	Socioeconomic status
SSA	Sub-Saharan-Africa
TB	Tuberculosis
Td	Tetanus and Diphtheria
USA	United States of America
VPDs	Vaccine-Preventable Diseases
WHO	World Health Organization

Glossary

BCG	Vaccine against tuberculosis
DPT	Vaccine against diphtheria, tetanus, pertussis
Hexa	Vaccine against diphtheria, tetanus, pertussis, polio, haemophilus influenza type b, hepatitis B
OPV	Oral vaccine against polio
PCV	Vaccine against pneumonia, meningitis and other pneumococcal diseases
Rota	Vaccine against rotavirus that causes diarrhoeal disease
Measles	Vaccine against the measles disease
Vaccine coverage	Proportion of children who received vaccines at a certain age, regardless of the timing of administration.
Vaccine timeliness	Proportion of children who have received age recommended vaccines within a specific time when a dose can be received early, timely, or late.

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1 INTRODUCTION

1.1 Background

Vaccines prevent and control infectious diseases, outbreaks and Antimicrobial Resistance (AMR) by preventing infections hence averting misuse and disuse of antibiotics [1]. The immunisation agenda 2030 (IA2030) describes the new immunisation goals which aim to "reach every child worldwide with life-saving vaccines by 2030" in efforts toward achieving Sustainable Development Goal (SDG) 3.b.1 target of universal vaccination coverage [2]. The effectiveness of vaccination includes the eradication of smallpox disease and the elimination and control of diseases including neonatal tetanus, guinea worms and measles in most parts of the world [3].

Though succeeded, the EPI is not without challenges; some Vaccine-Preventable Diseases (VPDs) for example, Tuberculosis (TB), pneumonia and diarrhoea still cause severe mortality and morbidity despite vaccines existing [3]. There has also been vaccine hesitancy fuelled by disinformation and misinformation and vaccine inequities which all affect vaccine coverage and immunity [4].

Vaccination coverage is the universal measure of performance of the EPI. The past decade, from 2010 to 2019, has seen plateauing in progress toward universal coverage [5]. Globally, 116 million children completed vaccination with a basic set of vaccines, 14 million children with zero dose coverage and 6 million partially vaccinated in 2019 [6]. In 2021, the global vaccine coverage decreased from 86% to 81% with an addition of 5 million completely unvaccinated children since 2019 [7]. On the other hand, Africa falls behind in access to vaccines with 1 in 5 African children missing basic vaccines [6]. This has been attributed to over 30 million under-five children getting VPDs each year and over 500,000 resulting deaths[8]. Although Gavi, the Vaccine Alliance, an international organisation committed to improving vaccine access in developing countries has been successful in closing the vaccine coverage gap with richer countries, in 2019, two-thirds of the zero-dose children were mainly from Low- and middle-income countries (LMCIs) [6]. This can be explained by social, economic, climate, political (including conflict), and health inequities [5]. These inequities have been increased by the new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes Coronavirus disease (COVID-19).

Declared a global pandemic in March 2020, COVID-19 has caused severe morbidity and mortality worldwide [9]. Due to the fragile health systems, the pandemic was expected to be detrimental in Africa, on the contrary, there have been lower than expected numbers of morbidity and mortality [10]. The COVID-19 incidence and mortality rates in Africa have been lower than the rates in High- Income Countries (HICs) [11]. Figure 1- 1 shows the burden of COVID-19 from the early stages of the pandemic in 2020 to 2022. HICs have had more cases and deaths than Africa throughout except in late August 2021 when the number of deaths in Africa surpassed those in HICs for a short period [12].

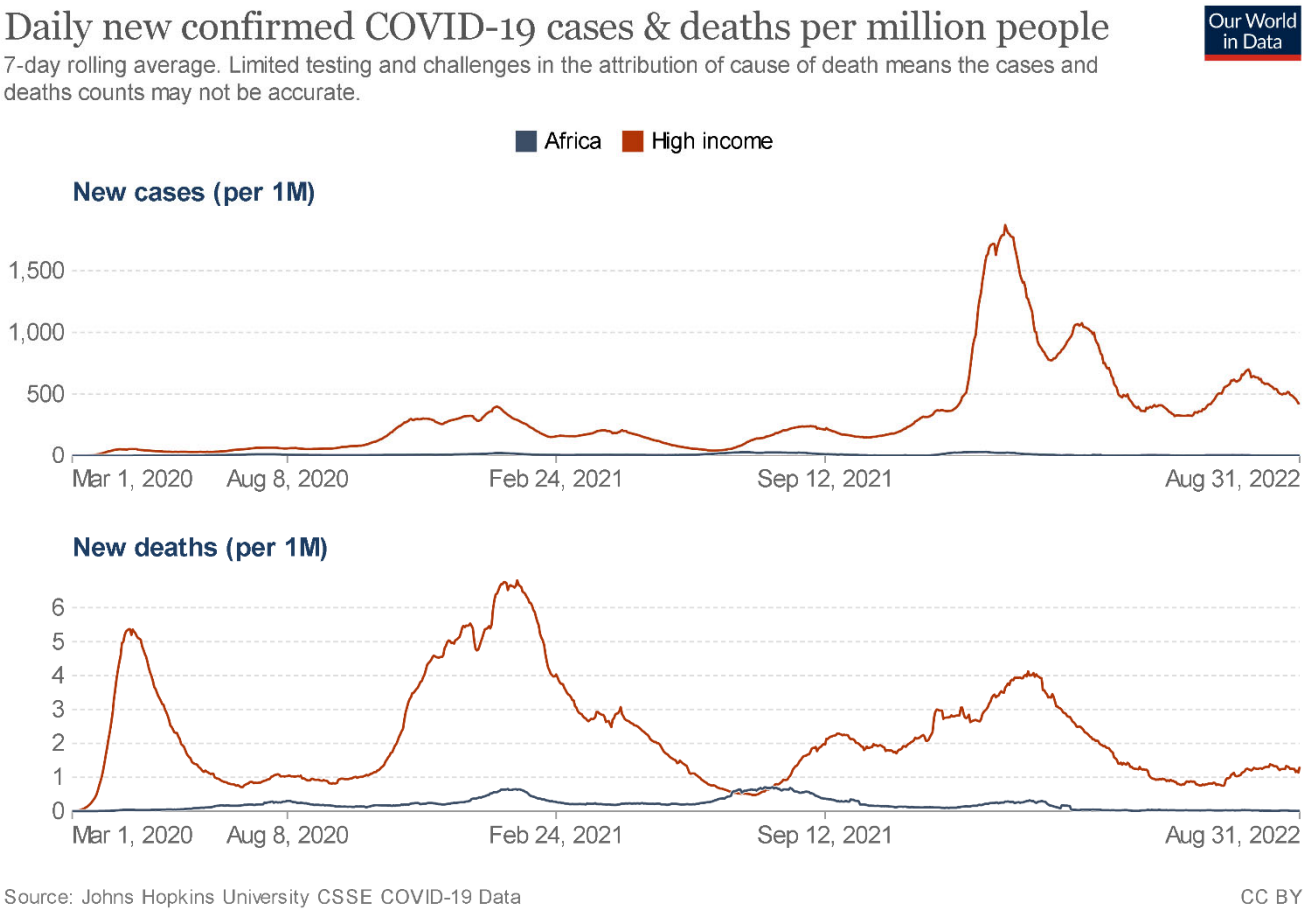


Figure 1- 1:The number of confirmed cases and deaths of COVID-19 from 2020 to 2022 in Africa and High-income countries (HICs)

South Africa was the most affected country in Africa with enormous morbidity and mortality [13,14]. Figure 1- 2 shows the number of COVID-19 cases from March 2020 early in the pandemic to the end of 2021 in the African continent. As highlighted in the figure, South Africa has had the highest number of confirmed incident cases in the continent at many time

points, compared to the other African countries.

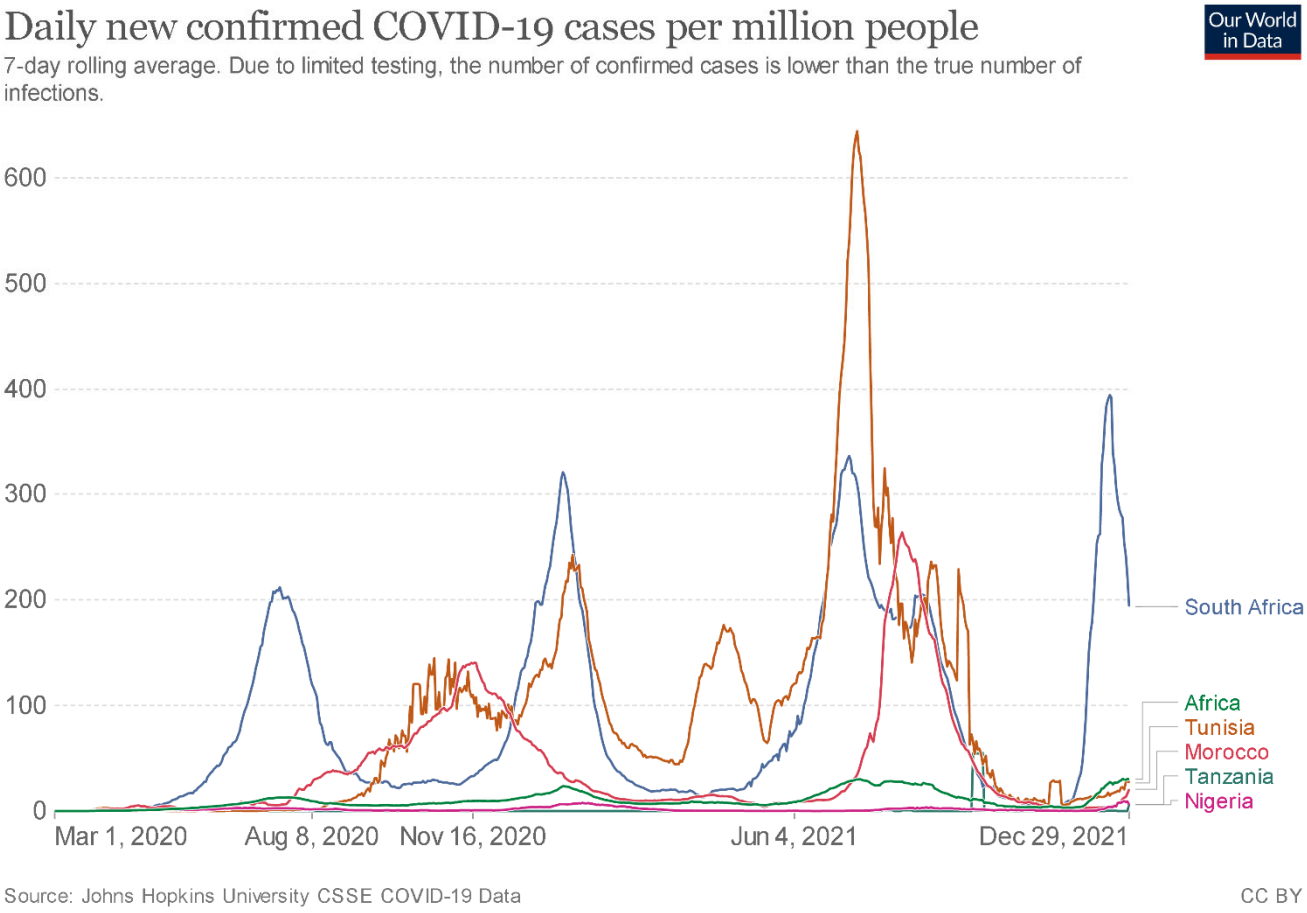


Figure 1- 2: Number of coronavirus (COVID-19) cases in the African continent as of March to December 2021, by country

As a result, different countries including South Africa adopted public health measures administered in different phases to control and prevent the spread of the infection, including physical distancing and lockdown [15,16]. This was to reduce pressure on the healthcare system and reduce spread. However, the system has still been overwhelmed [17].

There have been reports of a decline in vaccination coverage at the beginning of the pandemic and during the lockdown phases in SSA during the pandemic, with or without sustaining EPI services [18]. A study done in 15 African countries showed reduced vaccine coverage in 13 of the 15 countries with a huge decrease in countries that had poor vaccine coverage in the pre-pandemic period [19]. This may have affected progress towards the achievement of IA2030 coverage goals in South Africa. In efforts to ensure that the COVID-19 pandemic does not destroy the immunisation milestones gained through the Global Vaccine Action Plan (GVAP),

it is essential to monitor both vaccine coverage and timeliness during these unprecedented times to establish counteracting measures.

1.2 Literature review

1.2.1 Expanded Programme on Immunisation of South Africa (EPI-SA)

The EPI-SA was launched in 1974 together with the rest of the world and remained fragmented until 1994 when it was unified [20]. It started with the delivery of 6 antigens namely; tuberculosis, measles, diphtheria, whooping cough (pertussis), tetanus and poliomyelitis, currently expanded to 11 antigens adding; hepatitis B, Haemophilus influenzae type b (Hib), pneumococcal diseases, diarrhoea (caused by rotavirus) and the Human Papilloma Virus vaccine (HPV). Its goal is to prevent death and reduce morbidity from VPDs in the long run ensuring healthy life [21,22]. Vaccination services are provided at no cost by the National Department of Health (NDOH) through policies, procedures, and guidelines to support routine vaccination services provision across the country [22]. The EPI-SA has achieved notable successes in the last few decades, including the eradication of Polio, with its last wild polio case reported in 1989 [23]. It has also attained control of some diseases including tetanus, diphtheria and pertussis [22]. It established a surveillance system through the National Institute for Communicable Diseases (NICD) to study the impact of these vaccines on the incidence of disease and AMR [22]. Immunisation services have been continuously improved and provided. The EPI-SA vaccine schedule includes children from birth to 12 years. It provides vaccines that protect against different diseases

1.2.2 Diseases targeted by the EPI-SA

Poliomyelitis

It is an infectious disease caused by the *poliovirus*. There are three types of *polioviruses*, namely types 1, 2 and 3. The EPI-SA targets polio disease through the first and second dose of the Oral Polio Vaccine (OPV0 & OPV1 received at birth and 6 weeks of age respectively) and the hexa1 to hexa4 (received at 6, 10,14 weeks and 18 months of age) which has an intramuscular inactivated component of the polio vaccine with other vaccine antigens. Polio is one of the global target diseases for global eradication and there has been tremendous progress to eradicate polio with only 2 countries remaining (Pakistan and Afghanistan) to eliminate it before the pandemic [24,25]. There have been polio outbreaks in 2021/22 in Malawi, Mozambique (wild type 1) and England (Vaccine-derived poliovirus type 2); countries that had previously eliminated polio [26–28]. This could be explained as effects of the pandemic surfacing or increased polio surveillance with the coming of the COVID-19 pandemic which is less likely considering the strained essential health services in the pandemic times.

Tuberculosis (TB)

TB is an infectious disease that often affects the lungs similar to SARS-CoV-2 but also spreads to other parts of the body. It is caused by *Mycobacterium Tuberculosis (MTB)* and it is the world's top infectious killer, the leading cause of death in people with HIV and also a major contributor to antimicrobial resistance [29]. South Africa is among the top 8 countries with half of the TB cases in the world [30]. The EPI-SA targets TB through the Bacille Calmette-Guérin vaccine (BCG) given at birth. During the COVID-19 pandemic, TB deaths increased, fewer cases were diagnosed and treated and fewer resources were available for TB management hence reversing the good work that has been done over the years [31].

Pneumonia

Pneumonia is an infection of the lungs often caused by *Streptococcus pneumoniae*. It is one of the leading causes of under-five morbidity and mortality in the world [32,33]. The EPI-SA targets *S. pneumoniae* through the first, second and third doses of the Pneumococcal Conjugate Vaccine (PCV1, PCV2 & PCV3) given at 6-, 14 weeks and 9 months. The first, second third and fourth doses of the hexa (hexa1, hexa2, hexa3 & hexa4) vaccines contain antigens against *Haemophilus influenzae type b*, a bacterium that also causes pneumonia.

Diarrhoeal disease

This is an infectious disease that is among the top causes of under-five morbidity and mortality though the commonest in LMICs [32]. "*Rotaviruses are the most common cause of severe diarrhoeal disease in infants and young children worldwide and severe rotavirus gastroenteritis is largely limited to children aged 6–24 months* [34]." Introduced in the EPI-SA in 2009, rotavirus vaccines are given at 6 and 14 weeks of age.

Measles disease

A highly infectious acute illness caused by the *measles virus*. It is also one of the target diseases for global eradication [35,36]. The EPI-SA targets measles disease through the first and second doses of the measles conjugate vaccine, (MCV1 & MCV2) given at 6 and 12 months. Outbreaks of measles have been reported in Liberia, India, Pakistan and many more in 2021-2022 [37,38]. Even though the initial plan of eradicating it by 2015 failed, the objective of GVAP, of eliminating measles in five regions by 2020 has failed with the pandemic contributing as evidenced by measles outbreaks in Africa and Asia [39].

Tetanus, pertussis and diphtheria disease

The EPI-SA also cater for tetanus, pertussis and diphtheria diseases through *tetanus, pertussis and diphtheria* antigens in the hexa vaccines and *tetanus and diphtheria* antigens in Td booster doses given at 6 and 12 years.

Table 1- 1:Expanded Programme on Immunisation of South Africa vaccine schedule of children from birth to 12 years

Scheduled time	Vaccine dose
Birth	BCG
Birth	OPV0
6 weeks	Hexa1
6 weeks	OPV1
6 weeks	Rota1
6 weeks	PCV1
10 weeks	Hexa2
14 weeks	Hexa3
14 weeks	PCV2
14 weeks	Rota2
6 months	MCV1
9 months	PCV3

12 months	MCV2
18 months	Hexa4
6 years	Td
9 years	HPV
12 years	Td

Table 1- 1 shows the EPI-SA public vaccine schedule which includes children from birth to 12 years. This study will mostly look at vaccines given from birth to 18 months of age (BCG to hexa4

Vaccine timeliness, an important measure of the quality of performance of the EPI, influences the level of herd immunity among populations. Early doses risk suboptimal immunity, timely doses ensure that the required immunity is generated to fight disease at their prime or severity and delayed doses not only risk completion of the vaccine, it also leads to VPDs as children are not protected, in the end, more susceptible people and low level of herd immunity [40,41]. No standardised criteria for defining vaccine timeliness are available in Africa hence no consensus on the best way to measure it[41,42]. Different studies use different measurements of vaccine timeliness. A systematic review by Masters et.al defined vaccination timeliness in terms of up-to-date vaccination; where people receive vaccines by a specific threshold age, vaccination delay; vaccination measurement in either the age of vaccination or the time elapsed since the vaccine was recommended to be administered and vaccination administered within a defined time since a recommended age of vaccination [41]. Another recent study also found that there are three ways that most studies defined vaccine timeliness, including delayed vaccination in 99.5%, early vaccination in 21.9% and untimely vaccination in 9% of the studies [42].

South Africa recommends a public vaccine schedule as per Table 1- 1 and defines timeliness as per WHO guidelines [22,43]. A study was done in Western Cape and KwaZulu-Natal (KZN) in 2011, grouped vaccine timeliness as timely and untimely vaccination. It defined timely BCG doses as those administered from birth-8 weeks, OPV0 from birth-4 weeks, Hexa1 from 4 weeks-2 months, hexa3 from 12 weeks-6 months and hexa4 was undefined [44]

Another study done in Soweto and Pietermaritzburg in 2013, defined late vaccination as vaccines received > 4 weeks beyond the scheduled date [45]. An Eastern Cape study in 2016 defined timely vaccination as vaccines received on the scheduled date without considering buffer time [46]. A recent study in Western Cape in 2021 defined timely vaccination as receiving vaccines 5 days before and not longer than 28 days after the recommended age, early uptake as vaccines received earlier than 4 days before the recommended age and delayed uptake of vaccine doses as receiving vaccines > 28 days after the recommended schedule age [47] This shows lack of standardised guidelines on the criteria to use when defining timeliness to whether to categorise vaccines as timely or untimely, early or timely or delayed and the time bounds allowed in each category.

An immunisation catch-up schedule (refer to Table 1- 2) is available, derived from vaccine manufacturers' recommendations on who to receive vaccines in case of delayed or missed doses. The upper age limit shows children who if below it, should receive catch-up vaccination and if above it is age in-appropriate for vaccination [48].

Table 1- 2:Vaccine upper age limit recommendations for the catch-up of vaccines in the South African routine immunisation schedule

Vaccine dose	**Upper age limit per national schedule**
BCG	12 months
OPV	6 months
Hexa	59 months
Rota	24 weeks
MCV	None
PCV	72 months
Td	15 years

Table 1- 2 shows the immunisation catch-up schedule for the EPI-SA vaccines derived from vaccine manufacturers' recommendations on who to receive vaccines in case of delayed or missed doses. The upper age limit shows children who if below it, should receive catch-up vaccination and if above it, is age in-appropriate for vaccination. Of note is that measles can be received at any age.

1.2.3 COVID-19 and lockdowns in SA

SA was listed among African countries at the highest risk of COVID-19 importation and local transmission in early 2020 [49]. SA was hit with the most COVID-19 cases in Africa. Strict lockdown restrictions were imposed nationwide from level 5 to level 1; with level 5 having the toughest restrictions and level 1 having relaxed rules and indicating the low spread of infection [16]. This was done to reduce pressure on HCWs, control infection rate and allow time for the Department of Health (DoH) to prepare treatment and quarantine facilities [50]. The lockdown levels were adjusted over time throughout the years 2020 and 2021 depending on SARS-CoV-2 incidence rates.

Table 1- 3: Levels of lockdown and the alert levels in South Africa in 2020-2021

Level of lockdown	**Alert levels indication**	**Timelines**
Level 5	Most stringent rules- indicate a high COVID-19 spread with a low health system readiness.	26 March 2020 to 30 April 2020
Level 4	Least stringent rules than level 5- indicate a moderate to a high COVID-19 spread with a low to moderate health system readiness	1 May 2020 to 31 May 2020 Adjusted alert level 4 from 28 June to 25 July 2021.
Level 3	The least stringent rules than level 4- indicate a moderate COVID-19 spread with a moderate health system readiness	1 June 2020 to 17 August 2020 An adjusted alert level 3 from 29 December 2020 to 28 February 2021 Adjusted alert level 3 from 16 June to 27 June 2021. Adjusted alert level 3 from 26 July to 12 September 2021.
Level 2	The least stringent rules than level 3- indicate a moderate COVID-19 spread with a high health system readiness	18 August to 20 September 2020 Adjusted alert level 2 from 31 May to 15 June 2021. An adjusted alert level 2 from 13 September 2021
Level 1	Most relaxed rules- indicate a low COVID-19 spread with a high health system readiness	21 September 2020 to 28 Dec 2020 An adjusted alert level 1 from 1 March 2021 to 30 May 2021.

Table 1- 3 shows the different alert levels of lockdown in SA from Mar 2020 to Dec 2021 in response to the burden of the disease to reduce transmissibility. Levels of lockdown were changing with time according to the burden of disease to prolong the peak (net reproduction = 1) while making sure that there is a decreased burden on the health system [16].

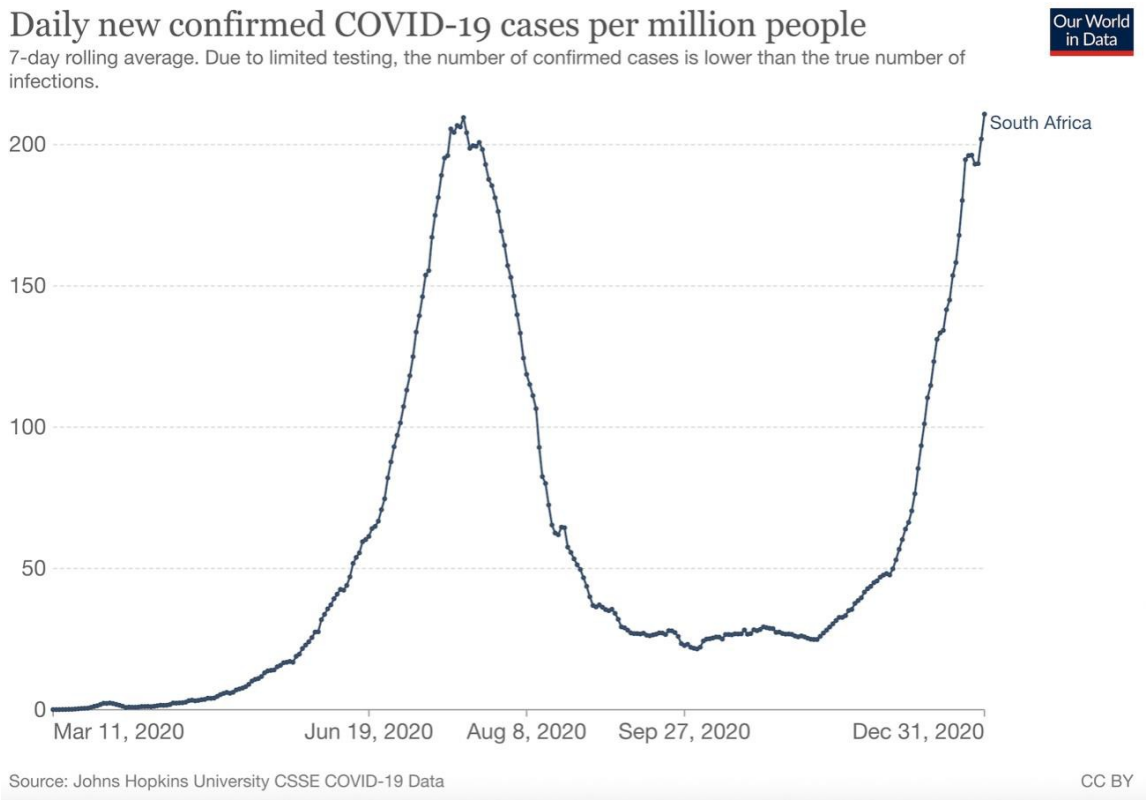


Figure 1- 1: Daily new confirmed COVID-19 cases per million people in South Africa from March 2020 to December 2020. Source: our world in data [51]

Figure 1- 1 shows peaks in the first two waves of the new COVID-19 cases/million in the early year of the pandemic. The first peak was reached around the end of July 2020 with over 200,000 cases/million. Subsequently, there was then a drop in the infections which led to less stringent control measures at level 3 of lockdown. The infection increased again (net reproduction > 1) around the end of December 2020 as people are usually celebrating during the festive season and there is increased social contact and mixing increasing the transmissibility of the infection

1.2.4 The possible impact of lockdowns on EPI-SA

In SA, there has been evidence of reduced access to child health care services including immunisation services in the primary healthcare centres creating vaccination backlogs [17,52] with the other health system areas being affected too. Vaccine coverage of MCV2 and PCV3 in SA decreased from 86% and 79% in 2019 to 83% and 76% respectively in 2020 among children which was below the WHO targets [53]. However, vaccine timeliness is not the same as vaccine coverage, as timeliness not only considers the reception of the vaccine but also the age recommendation and appropriateness of the child to receive the dosage. Studies found

that vaccine coverage estimation methods largely mask vaccine timeliness while showing high or constant national coverage [54,55]. Mthiyane et.al found that even though vaccine coverage was high in Soweto and Pietermaritzburg, some of the vaccine doses were received late [45]. Other vaccine timeliness studies in Western Cape, SA found an increased delay in timeliness with decreased coverage as age increases with delay in receipt of subsequent doses [47]. All of these highlight the gaps of only monitoring coverage instead of both timeliness and coverage. Therefore, using both indicators to measure the effective performance of routine vaccines is vital. During the pandemic, despite the continuation of immunisation services in SA [56], the affected health system, vaccine coverage and lockdown measures and other already existing factors could have exacerbated vaccine timeliness problems. Delayed and early vaccine dose timeliness could result in few immune people and an increased susceptible population leading to an increased risk of VPDs which the EPI-SA has successfully controlled in the past destroying all the previous efforts [57] toward universal vaccination coverage. However, nothing has been published on vaccine timeliness during the pandemic in SA.

1.3 Problem statement

Despite the continuation of immunisation services during the pandemic, a study done in KZN province, SA, showed that access to child health care services has been disrupted during lockdown (especially the first months) with the EPI being one of the important elements affected [17]. This disruption reduced vaccine coverage of MCV2 and PCV3 nationally from 86% and 79% in 2019 to 83% and 76% respectively in 2020 risking VPDs [53]. Areas such as KZN, North West, Johannesburg and Limpopo did not reach their vaccine coverage targets for MCV1 & MCV2 and hexa vaccines [58]. The effect of the COVID-19 pandemic on vaccine timeliness in SA is unknown. We, therefore, hypothesize that the timing of infant and child vaccination schedules may have been negatively affected during the pandemic and lockdown period as the world was at a standstill. Previous outbreaks for instance Ebola demonstrated the costs of suspending essential health services while implementing the Ebola outbreak response [59]. Therefore, to test this hypothesis, we aim to assess whether the SARS-CoV-2 pandemic has affected the timeliness of vaccine coverage. Consequently, this will help us to measure the performance and quality of EPI-SA during the pandemic. This will assist future planning and evaluation of EPI-SA for activities, for example, Supplementary Immunisation Activities (SIAs) and catch-up campaigns for resilience during future outbreaks. Our research findings will be relevant to discovering the trends, disparities,

and inequities in running EPI programs during public health emergencies to find strategies for overcoming them in SA.

1.4 Study objectives

1.4.1 Aim/main purpose

The main purpose of the study was to look at the possible impact of the COVID-19 pandemic on the timeliness of routine immunisation in Soweto and Thembelihle, South Africa.

1.4.2 Research question

What was the effect of the COVID-19 pandemic on the timeliness of routine immunisation of children 0-23 months of age in Soweto and Thembelihle?

1.4.3 Primary objectives

1. To determine the proportion of child vaccinations received on time at birth, 6-, 10- & 14- weeks, 6-, 9- 12- and 18- months of age during the COVID-19 pandemic and lockdown (2020) compared to children vaccinated before the COVID-19 pandemic (2018/2019).
2. To determine the proportion of child vaccinations received early, that is, before the scheduled date, and late, that is after a fixed grace period following the scheduled date (birth, 6-, 10- & 14- weeks, 6-, 9- 12- and 18- months of age) in children vaccinated during the COVID-19 pandemic and lockdown compared to children vaccinated before the COVID- 19 pandemic.
3. To determine the proportion of missed doses during the COVID-19 pandemic and lockdown compared to before the COVID-19 pandemic.
4. To investigate the reasons associated with missed child vaccinations during the year 2020 compared to the years 2018/2019.

2 METHODOLOGY

2.1 Ethics

Ethics approval for this secondary analysis was obtained on 13 September 2021 reference number M210630 from the University of the Witwatersrand Human Research Ethics Committee (Med) (HREC). Permission was granted by Vaccines and Infectious Disease Analytics (VIDA) Research Unit leads of Child Health and Mortality Prevention Surveillance system (CHAMPS) (Professor Shabir Madhi) and the Health and Demographic Surveillance System (HDSS) principal investigator and gatekeeper Dr Portia Mutevedzi to use the HDSS/CHAMPS data for secondary analysis.

Data were collected with participant consent for HDSS/ CHAMPS. No additional Informed consent was required. Privacy was ensured by using de-identified and non-anonymised data. The primary study was approved by the University of Witwatersrand's Human Ethics Research Committee with reference number 170216.

2.2 Study design

This is a retrospective cohort study describing the impact of the COVID-19 pandemic and lockdown on the timeliness of scheduled vaccination doses and reasons for missed vaccinations. A secondary analysis of longitudinal vaccination data collected from Soweto and Thembelihle HDSS was done.

2.3 Study setting

Soweto and Thembelihle are in Johannesburg. Soweto is an urban township mostly occupied by Black African people with an estimated population of 1.3 million, including 125,000 children under 5 years of age in around 100 clusters and covering an area of 200 km2 [60]. Thembelihle is a local municipality, and its adjoining areas are informal urban settlements with a population of >20 000. The HDSS catchment areas cover 9 mostly non-contiguous clusters of low socioeconomic status, with an area of 17.7 km and 19.0 km in Soweto and Thembelihle respectively. The population under surveillance in 2018 was 123 225 individuals in 35 302
households [60].

2.4 Data source and study population

The study used data from an HDSS done in Soweto and Thembelihle which collects data on geographic indicators, pregnancy history, pregnancy outcomes, demographic and socioeconomic status information, child health, and migration. With 40 staff members 2 rounds of household (HH) visits are done per year using 3 questionnaires on women's health (women questionnaire), HH information (HH questionnaire) and under-5 children (children questionnaire) to determine the morbidity and mortality among pregnant women and children <5 years of age and provide intervention programs aimed at improving the health and well-being of the population under surveillance. Nine clusters (eight from Soweto, one from Thembelihle) were selected for surveillance based on two eligibility criteria: areas with low SES and under- 5 and overall mortality in SA among people living in urban informal settlements (at least 50 deaths per 1000 live births in Soweto and high reported deaths in under-5 children in Thembelihle) [59–61].

Approximately 65% of the population in the selected clusters were recruited into the HDSS, with 35% not recruited due to the unavailability of some participants and boundary issues. A careful comparative analysis of recruited and non-recruited individuals showed no difference in characteristics, composition and distribution [61]. The HDSS had a HH retention rate of 95% in 2019-20.

The HDSS started in Soweto in 2017 and later in mid-2018 extended to Thembelihle where baseline data was collected for every child and also for new children who enter the survey, then several follow-up rounds of data collection are done each year (approximately two), to update the information [61].

This analysis looked at data that were collected from the under-5 children questionnaire where five rounds of data were collected since the beginning of the HDSS. Data on demographics of the children and caregiver information, vaccination status (type, dose of vaccine, date received) and the reasons provided by caregivers for missed doses were used.

2.5 Study sample size

A complete enumeration of 2,888 eligible study participants (children between 0 & 23 months) was used.

2.6 Study selection criteria

The current study included every child 0-23 months from the HDSS born between Jan 2018 to 31st December 2020. Children were excluded from the analysis if they did not have dates or had inconsistent dates which could not be cross-checked and those with oral recall data.

2.7 Data management

In this study, the data were extracted from the database and imported into STATA software, version 17.0 (Stata Corp, Lake way Drive, College Station, TX, USA). Data merging was performed, and all participant identifiers were removed from the data. The files with data are password protected and stored in an encrypted folder, and they will be deposited in a repository. Data were analysed up to data collected on Dec 2020 as this was the only data available at the time of data extraction and access. Data were cleaned through data validity checks, duplicates, outliers, and checking for inconsistencies and missing data. Data values with missing data were excluded from the analysis.

2.8 Outcome measures

The data were used to compare the timeliness of vaccines given and the reasons for missed vaccination before the COVID-19 pandemic (2018/2019) and during the COVID-19 pandemic and lockdown (2020) when pandemic mitigation measures were in place in SA. The 6 vaccines (BCG, OPV, hexa, PCV, rota, MCV) are given from birth to 18 months as part of the EPI-SA according to a recommended schedule. The primary outcome was vaccine timeliness. Vaccine timeliness was categorized as early/ Invalid, on-time (timely) doses, and delayed (late) doses. Early doses were calculated by dividing the number of children aged 0-23 months who received the vaccine before the recommended age or minimum interval from the previous dose for the vaccine of interest as specified in the EPI-SA schedule by the total number of children with a recorded date for the particular dose. All early doses were invalid but not all invalid doses were early as some invalids were from age-inappropriate doses. Timely doses were calculated by dividing the number of children aged 0-23 months who received the vaccine at 0 to <= 28 days after the recommended age by the total number of children with a recorded date for the particular dose. Delayed doses were calculated by dividing the number of children aged 0-23 months who received the vaccine at >28 days after the recommended age to the upper limit age for catch-up vaccine eligibility (refer to Table 1- 2) by the total number of children with a recorded date for the particular dose.

Age-inappropriate doses were those administered beyond the upper limit age for the catch-up vaccine eligibility period per SA catch-up immunisation guidelines. All age-inappropriate doses were invalid in this study as they were administered at a time beyond the vaccine manufacturer's recommendations. Missed doses children were defined as children who did not receive the vaccination dose for the specific vaccine (for each specific vaccine dose not received). Reasons for missed vaccination were also listed between the years 2018/2019 and 2020. For multi-dose vaccines, completeness was defined as the proportion of children who received all doses of the specific vaccine. Table 2- 1 fully describes vaccine timeliness bounds about the EPI-SA schedule from which our study population uses. Even though different literature uses different periods for the timeliness, as there is no consensus on a standard definition of vaccine timeliness, we used 28 days as per WHO guidelines which EPI-SA uses [62]. In general, timeliness assesses whether a child was vaccinated on the recommended schedule, while completeness assesses whether a child received all specific vaccine doses.

Table 2- 1: Vaccine timeliness bounds (early/timely/delayed/ age- inappropriate) for different doses given in the Expanded Programme on Immunisation of South Africa

Age at administration (recommended by EPI-SA)	**Vaccine dose**	**Early/invalid (days)**	**timely (recommended age plus 28 days)**	**Late/delayed (days)**	**Age-inappropriate**
Birth	BCG	N/A	0- 28 days	>28 days to 365 days	> 365
Birth	OPV0	N/A	0- 28 days	>28 days to 181 days	> 181 days
6 weeks	Hexa1	0 to 41 days	42-70 days	>70 days to 1,794 days	> 1,794
6 weeks	OPV1	0 to 41 days	42-70 days	>70 days to 181 days	> 181 days
6 weeks	Rota1	0 to 41 days	42-70 days	>70 days to 168 days	> 168 days
6 weeks	PCV1	0 to 41 days	42-70 days	>70 days to 2,190 days	> 2,190 days
10 weeks	Hexa2	0-69 days	70-98 days	>98 days to 1,794 days	> 1,794 days
14 weeks	Hexa3	0-97 days	98-126 days	>126 days to 1,794 days	> 1,794 days
14 weeks	Rota2	0-97 days	98-126 days	>126 days to 168 days	> 168 days
14 weeks	PCV2	0-97 days	98-126 days	>126 days to 2,190 days	>2,190 days
6 months	MCV1	0-181 days	182-210 days	>210 days	N/A
9 months	PCV3	0-269 days	270-298 days	>298 days to 2,190 days	> 2,190 days
12 months	MCV2	0-364 days	365-393 days	>393 days	N/A
18 months	Hexa4	0-546 days	547-575 days	>575 days to 1,794 days	> 1,794 days

N/A where definition doesn't apply as there no time limits for receiving MCV Age-inappropriateness will only be assessed for BCG/OPV and rota

2.9 Analysis

The dataset used for data analysis had 39,141 observations and 100 variables. Using the inclusion criteria of children who were 0-23 months old between the 2018 and 2020 period and who had vaccine cards, data of 2888 participants were extracted for analysis. The data were checked for inconsistencies, for instance, receiving a certain vaccine before birth, mixing-up of dates of vaccines reception such as measles vaccine received before BCG vaccine. After all the inconsistencies were rectified, the data were certified as cleaned and ready for analysis.

New variables were generated. For example, age in days/months/years at which a child received a vaccine, vaccine reception timeliness (early/timely/late), vaccine eligibility (yes/no) based on the age at which a child received a particular vaccine, vaccine received (yes/no) based on the information on the vaccine cards, multi-dose vaccine coverage, reasons for not receiving the vaccines. For those who missed vaccination, eligibility of vaccine reception dates was created based on dates of birth to categorize them into pre-pandemic and pandemic periods to quantify the vaccination missed opportunities between the two periods. Furthermore, the study sample was disaggregated into two groups (0-11 months and 12-23 months). Children who were vaccinated in both years 2018/19 and 2020 for example a child who was born in 2019 and received earlier vaccines in 2019 and later vaccines in 2020 were included in both the 2018-2019 group and the 2020 group.

The data analysis was done in two stages. First, descriptive analysis, where proportions and frequencies for categorical variables were calculated and cumulative plots were created to depict the coverage of selected vaccines across ages in months for 0-11 months and 12-23 months groups. Second, univariable univariate analysis was performed to determine the presence or absence of association between outcome(s) i.e. timeliness and explanatory variable(s), particularly the pandemic/Pre-pandemic period variable. Pearson chi-square tests or Fisher's exact tests were used in the determination of the presence of evidence of associations because the outcomes and the exposures were all categorical. Fisher's exact tests were mainly employed when at least one of the expected frequencies in the cross-tabulations was below 5, otherwise, Pearson chi-square tests were the main tests for the associations at the alpha 0.05 level.

Table 2- 2: The analysis strategy for each outcome in the study

Outcome	**Analysis**
The proportion of child vaccinations received early / timely and late for all vaccines during the COVID-19 pandemic) compared to children vaccinated before the COVID-19 pandemic (2018/2019).	From the information on cards, new variables called age in days/months/years at which a child received a vaccine was generated by subtracting birth date from the date of vaccine receipt. These were then grouped as (early/timely/late) timeliness (outcome), referencing Table 2- 1 Using the date of vaccine receipt, we also grouped the children into those who received each specific vaccine dose in 2018/2019 and 2020 (exposure) The variables were then tabulated in Stata using either chi-square tests or Fisher's exact tests to determine the evidence of association.
The proportion of complete doses among the multi-dose vaccine.	Complete vaccination variable was generated from those who received all doses of the specific vaccine for the multiple-dose vaccines including OPV/Hexa/PCV against all children who were eligible to receive the specific multi-dose vaccine
The proportion of missed doses during the COVID-19 pandemic and lockdown compared to before the COVID-19 pandemic.	Eligibility of vaccine reception dates variable was created based on dates of birth and assumed expected age of vaccination. The proportion of children eligible for the vaccine in the specific time who missed doses was calculated.
Reasons associated with missed child vaccinations during the year 2020 compared to the years 2018/2019.	For those who missed vaccination; for each vaccine dose, the proportion of each reason for missing vaccination was calculated.

3 RESULTS

In this chapter, a description of the participants is presented first, followed by the results of each objective. Overall, there were 39,141 children in the study, of which 5385 children had vaccination cards. There were 5,140 children born between 2018 and 2020 and from these only 2,888 children were eligible for the analysis; 1,427 of the eligible children were born in the pre-pandemic period and 1461 in the pandemic period. Out of those eligible 1659 (57.4%) were girls.

Table 3- 1:Number of children with specific vaccine dates on their vaccination cards in the study

Vaccine dose	**Number of children with vaccination dates on the vaccination card**
BCG	2,805
OPV0	2,795
OPV1	2,598
Hexa1	2,595
Rota1	2,596
PCV1	2,595
Hexa2	2,450
Hexa3	2,272.
PCV2	2,267
Rota2	2,266
MCV1	1,857
PCV3	1,312
MCV2	883
Hexa4	278

Table 3- 1 shows the number of children with vaccination dates on the vaccination card for each vaccine. The number of children with BCG vaccine dates on the card was greater than the OPV0 vaccine despite both being scheduled on the same day (at birth). For the six weeks doses (OPV1/ Hexa1/ Rota1/ PCV1), the number of children with vaccine dates on the card was similar. Likewise, the number of children with vaccine dates on their card for the14 weeks vaccines (Hexa3/ Rota2/ PCV2). The number of dates captured on the vaccination card decreased as the children received BCG to hexa4.

The overall proportions of timeliness are highlighted for BCG, hexa1 and hexa3 as follows: for children who had timely vaccination, 97% (2,635) was for BCG, 83% (2,088) for hexa1 and 80% (1,705) for hexa3. For late vaccination, 3% (87) for BCG, 6% (143) for hexa1 and 11% (229) were delayed for hexa3. For age-inappropriate vaccinations 0.3% (7) for BCG, none for hexa1 and hexa3. For early vaccinations 11% (283) for hexa1 and 9% (196) for hexa3 (Table 3- 2).

Table 3- 2: Timeliness proportions (early/timely/ late/ Age inappropriate) for each vaccine dose of the EPI-SA

in children 0-23 months from Soweto and Thembelihle

Vaccines	Number of children aged 0-23 received vaccine with dates	Early n (%)	Timely n (%)	Late n (%)	Age in-appropriate n (%)
BCG	2,729	N/A	2,635 (96.6)	87 (3.2)	7 (0.3)
OPV0	2,729	N/A	2,608 (95.6)	94 (3.4)	27 (1)
OPV1	2,489	318 (12.8)	2,051 (82.4)	106 (4.3)	14 (0.6)
Hexa1	2,514	283 (11.3)	2,088 (83.1)	143 (5.7)	N/A
Rota1	2,514	280 (11.1)	2,117 (84.2)	101 (4.0)	16 (0.6)
PCV1	2,511	276 (11.0)	2,113 (84.2)	122 (4.9)	N/A
Hexa2	2,339	239 (10.2)	1,880 (80.4)	220 (9.4)	N/A
Hexa3	2,130	196 (9.2)	1,705 (80.1)	229 (10.8)	N/A
PCV2	2,151	214(10.0)	1,711 (79.5)	226 (10.5)	N/A
Rota2	2,132	259 (12.2)	1,662 (78.0)	161 (7.6)	50 (2.4)
MCV1	1,718	200 (11.6)	1,337 (77.8)	181 (10.5)	N/A
PCV3	1,174	133 (11.3)	919 (78.3)	122 (10.4)	N/A
MCV2	770	78 (10.1)	603 (78.3)	89 (11.6)	N/A
Hexa4	232	42 (18.1)	177 (76.3)	13 (5.6)	N/A
N/A where definition doesn't apply as BCG and OPV0 start at birth and there are no time limits for receiving MCV, PCV and hexa					

Figure 3- 1 shows the cumulative vaccine timeliness coverage for BCG/hexa1/hexa3 in children aged 0-11 months in the study from 2018-2020. For BCG the median timely vaccination was 6 months, and it increased constantly until 10 months when there was a shallower increase in timely vaccination to 11 months. The median delay for BCG was at 7 months beyond which there were differences in steepness of the delay. About 50% of the children received Hexa1 early by 7.1 months, timely by 6.5 months and delayed vaccines by 7.2 months. The median early, timely and late coverage for hexa3 was 6.5, 6.3 and 8.5 months.

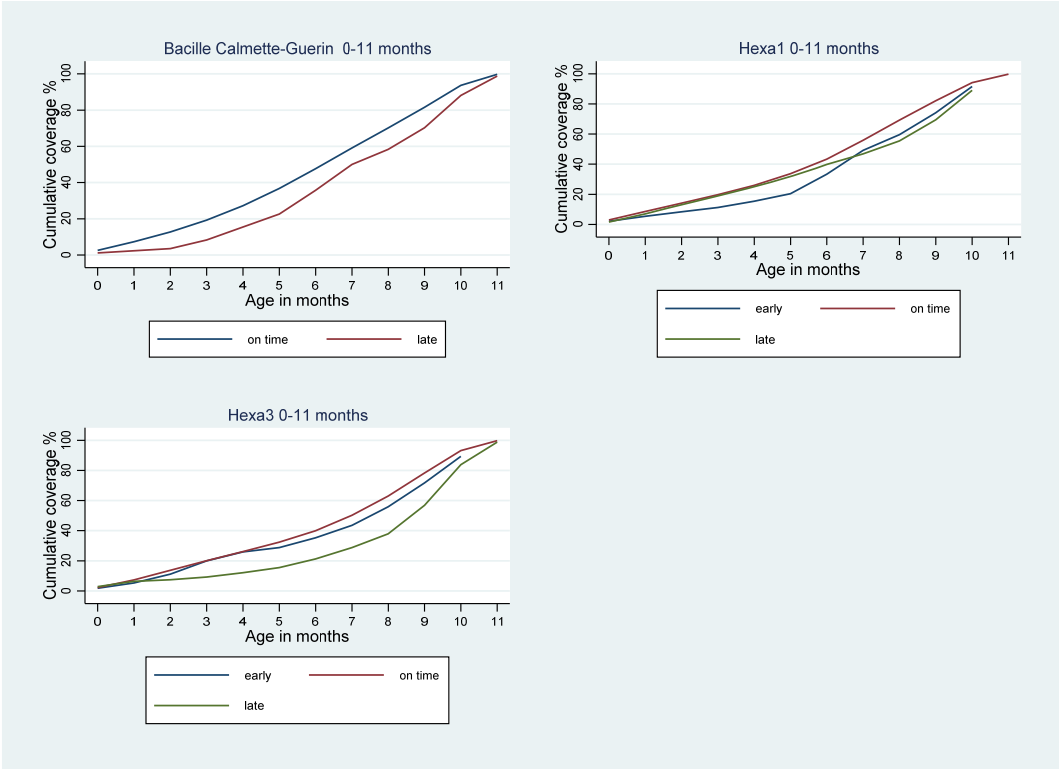


Figure 3- 1: shows the cumulative vaccine timeliness coverage for BCG/hexa1/hexa3 in children aged 0-11 months in the study from 2018-2020

Figure 3- 2 shows the cumulative vaccine timeliness coverage for PCV3/MCV2/hexa4 in children aged 12-23 months from Soweto and Thembelihle from 2018-2020**.** The median timely coverage for PCV3 was at 18 months after which there was a constant increase. The median delay for PCV3 was at 18.1 after which there was a steep increase in the coverage with varied velocities and early timeliness was at 18.5 months after which there was a constant increase. About 50% of the children received MCV2 timely at 18 months, early at 18.5 and late at 19.2 months. The median timely coverage for the hexa4 is at 18.8 months, early and late at 19 months.

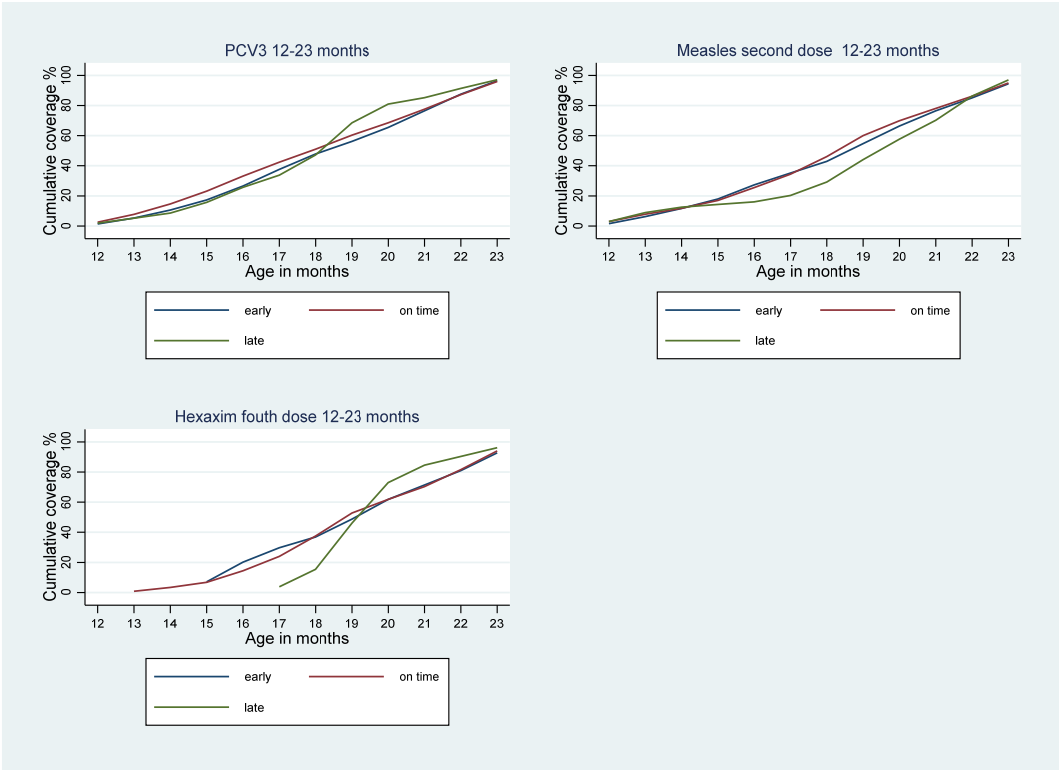


Figure 3- 2: shows the cumulative vaccine timeliness coverage for PCV3/MCV2/hexa4 in children aged 12- 23 months from 2018-2020

Objectives one and two: To determine the proportion of child vaccinations received early/ timely and late in the pre-pandemic and pandemic periods.

Table 3- 3 displays timeliness coverage for six vaccine doses which were selected to highlight the associations between Pre-pandemic and pandemic periods. While the two vaccines showed no differences in the percentages of timelessness between the two periods, the other four vaccines, indicated differences in the proportions of timeliness between pandemic and pre-pandemic times.

The proportions of timeliness (timely and late) of BCG between the two periods were similar (p=0.783). For instance, 96.9% (1251) had timely vaccination in pre- pandemic versus 96.7% (1384) during the pandemic. Late vaccination, on the other hand, was received by 40 (3.1%) pre-pandemic vs 47 (3.3%) during the pandemic.

Again, there were no significant differences between the periods under study in terms of timeliness for hexa1 (p=0.050); early Hexa1 doses were received by 13% (137) in pre-pandemic time against 10% (146) in the pandemic. In contrast, 857 children (81.6%) had timely vaccination before the pandemic versus 1231 (84%) during the pandemic. As for late

vaccination 5.3% (56) got it in pre-pandemic time against 5.9% (87) during the pandemic.

Between the two periods, the proportions of timeliness for PCV3, hexa3, hexa4 and MCV2 vaccines had significant differences whether early, timely or late. at P-values of $p<0.001$, $p<0.001$, $p=0.013$ and $p<0.001$ respectively. Generally, there were higher doses of vaccines received early in the pre-pandemic time than the pandemic time (all four vaccine doses). On the contrary, all vaccine doses were more delayed during the pandemic time than the pre-pandemic time. And three doses had better timeliness during the pandemic except for hexa3 which had better timeliness during the pre-pandemic.

The proportion of children that received PCV3 earlier was higher in the pre-pandemic period at 32.5% (39) than in the pandemic period at 8.9% (94). More children were vaccinated timely in the pandemic period 79.6% (839) than during the pre-pandemic period 66.7% (80).

Hexa3 early timeliness in pre-pandemic time was greater than 86 (11.8%) during the pandemic 110 (7.9%). The vaccine was more delayed in the pandemic season 174 (12.5%) than the pre-pandemic season 55 (7.5%).

On the other hand, the proportion of children that received early hexa4 was higher pre-pandemically 3 (100%) than those that received in the pandemic 39 (17.0%). As for timely vaccination, the pandemic period had better timelines 177 (77.3%) than the pre-pandemic period 0 (0.0%). This could be biased due to the small sample size.

MCV2 early proportions were greater in pre-pandemic time 11 (100%) than in pandemic time 67 (8.8%). It had better timely doses in the pandemic 603 (79.5%) times than in pre-pandemic time. (Table 3.2). Further associations are shown in appendix 1.

Table 3- 3: Associations between period and vaccine timeliness coverage for selected six vaccine doses

Vaccine Dose	**Pre-pandemic n (%)**	**Pandemic n (%)**	**P-value**
BCG			
Timely	1,251(96.9)	1,384(96.7)	0.783†
Late	40(3.1)	47(3.3)	
Total	1,291 (100)	1,431(100)	
Hexa1			
Early	137(13.1)	146(10.0)	0.050†
Timely	857(81.6)	1,231(84.1)	
Late	56(5.3)	87(5.9)	
Total	1,050(100)	1,464(100)	

Hexa3			
Early	86 (11.8)	110 (7.9)	<0.001†
Timely	591(80.7)	1,114(79.7)	
Late	55(7.5)	174 (12.5)	
Total	732(100)	1,398(100)	
PCV3			
Early	39 (32.5)	94 (8.9)	<0.001†
Timely	80 (66.7)	839 (79.6)	
Late	1(0.8)	121 (11.5)	
Total	120(100)	1,054 (100)	
MCV2			
Early	11(100)	67 (8.8)	<0.001*
Timely	0(0.0)	603 (79.5)	
Late	0(0.0)	89 (11.7)	
Total	11(100)	759 (100)	
Hexa4			
Early	3(100)	39 (17.0)	0.013*
Timely	0(0.0)	177 (77.3)	
Late	0(0.0)	13(5.7)	
Total	3(100)	229(100)	
*Fisher's exact test †Pearson chi-square			

Multi-dose vaccination coverage for OPV (0 &1), hexa (1-4), PCV (1-3), rota (1 & 2) and MCV (1&2) is presented in Table 3- 4. About 2511 (88%) children received both doses of OPV, 234

(9%) got all doses of hexa. For PCV, 1180 (47%) had all doses, 2095 (85%) children were vaccinated with all rota doses and 763 (48%) got both MCV doses.

Table 3- 4: Complete vaccination coverage for multi-dose routine vaccines in 2018-2020

Vaccine dose	**complete vaccination coverage n (%)**
OPV0-1	2511 (88.4)
Hexa 1-4	234 (9.3)
PCV1-3	1,180 (46.7)
Rota 1-2	2,095 (84.6)
MCV 1-2	763 (47.8)

Objective three: To determine the proportion of missed doses during the COVID- 19 pandemic and lockdown compared to before the COVID-19 pandemic.

The proportions of children who missed doses between the two periods were similar in all vaccines except MCV1 at a p-value of 0.007. MCV1 doses were missed more in the pandemic period 50 (7.2%) than in the pre-pandemic period 50 (4.3%). There was an absence of missed doses for children in the pandemic period for hexa4 (Table 3- 5).

Table 3- 5: Proportions of missed doses in children aged 0-23 months from Soweto and Thembelihle in 2018-2020

Vaccine dose	Missed doses pre- pandemic n (%)	Missed doses pandemic n (%)	P value
BCG	17 (1.3)	11 (0.8)	0.182
OPV0	12 (0.9)	11 (0.8)	0.691
OPV1	23 (1.7)	14 (1.1)	0.201
Hexa1	21 (1.6)	14 (1.1)	0.317
Rota1	19 (1.4)	12 (1.0)	0.278
PCV1	18 (1.3)	13 (1.0)	0.469
Hexa2	35 (2.7)	20 (1.8)	0.140
Hexa3	47 (3.8)	30 (3.0)	0.298
PCV2	34 (2.7)	30 (3.0)	0.742
Rota2	33 (2.6)	31 (3.1)	0.567
MCV1	50 (4.3)	50 (7.2)	0.007
PCV3	74 (7.6)	30 (9.0)	0.397
MCV2	76 (10.8)	12 (6.6)	0.088
Hexa4	35 (12.6)	-	-

Objective four: To investigate the reasons associated with missed child vaccinations during the year 2020 compared to the years 2018/2019.

In Table 3- 6, hexa3, rota2, PCV2 and PCV3 reasons' proportions for missing vaccinations were different for the two periods at P values of <0.001, <0.001, 0.007 and 0.008 respectively.

Health facility reasons were the commonest reasons for missing hexa3 in the pre-pandemic period compared to child illness in the pandemic period while for PCV3, primary caregiver reasons were the commonest reasons in pre-pandemic in comparison with COVID-19-related reasons during the pandemic time. Primary caregiver reasons were the commonest reasons for missing rota2 vaccine dose in the pre-pandemic in contrast with child illness in the pandemic period. Finally, for PCV2, primary caregiver reasons were the commonest reasons in pre-pandemic 11 (57.9%) compared to child illness in the pandemic period 8 (47.1%).

The frequencies for the reasons for missing vaccinations for the rest of the vaccines ((OPV (0 & 1), hexa (1 & 2), PCV1 and rota1) were similar between the two time periods.

Table 3- 6: Reasons for missed vaccinations for all vaccine doses in both periods among children 0-23 months in

Soweto and Thembelihle

Reasons for missed vaccines	Pre-pandemic	pandemic	P value
OPV0			0.440
Health facility	5(83.3)	7(70.0)	
Primary caregiver	1(16.7)	0(0.0)	
Child illness	0(0.0)	1(10.0)	
COVID-19 related	0(0.0)	2(20.0)	
Total	6(100)	10(100)	
OPV1			
Health facility	6(50.0)	1(12.5)	0.235
Primary caregiver	5(41.7)	4(50.0)	
Child illness	1(8.3)	2(25.0)	
COVID-19 related	0(0.0)	1(12.5)	
Total	12(100)	8(100)	
Hexa1			0.658
Health facility	4(36.4)	2(22.2)	
Primary caregiver	5(45.5)	3(33.3)	
Child illness	2(18.2)	3(33.3)	
COVID-19 related	0(0.0)	1(11.1)	
Total	11(100)	9(100)	
Rota1			0.204
Health facility	3(37.5)	0(0.0)	
Primary caregiver	4(50.0)	4(50.0)	
Child illness	1(12.5)	3(37.5)	
COVID-19 related	0(0.0)	1(12.5)	
Total	8(100)	8(100)	
PCV1			1.000
Health facility	1(16.7)	0(0.0)	
Primary caregiver	4(66.7)	5(62.5)	
Child illness	1(16.7)	2(25.0)	
COVID-19 related	0(0.0)	1(12.5)	
Total	6(100)	8(100)	
Hexa2			0.129
Health facility	4(22.2)	4(26.7)	
Primary caregiver	12(66.7)	5(33.3)	
Child illness	2(11.1)	4(26.7)	
COVID-19 related	0(0.0)	2(13.3)	
Total	18(100)	15(100)	
Hexa3			<0.001
Health facility	15(50.0)	1(5.6)	
Primary caregiver	13(43.3)	6(33.3)	
Child illness	2(6.7)	8(44.4)	
COVID-19 related	0(0.0)	3(16.7)	
Total	30(100)	18(100)	
PCV2			<0.001
Health facility	7(36.8)	0(0.0)	
Primary caregiver	11(57.9)	6(35.3)	
Child illness	1(5.3)	8(47.1)	
COVID-19 related	0(0.0)	3(17.7)	
Total	19(100)	17(100)	
Rota2			
Health facility	3(17.7)	2(10.5)	0.007

Primary caregiver	13(76.5)	6(31.6)	
Child illness	1(5.9)	8(42.1)	
COVID-19 related	0(0.0)	3(15.8)	
Total	17(100)	19(100)	
PCV3			0.008
Health facility	1(14.3)	18(29.0)	
Primary caregiver	5(71.4)	11(17.7)	
Child illness	1(14.3)	8(12.9)	
COVID-19 related	0(0.0)	25(40.3)	
Total	7(100)	62(100)	

4 DISCUSSION

This study assessed the timeliness of infant and child vaccination schedules in children aged 0-23 months from selected clusters in Soweto and Thembelihle, SA. In general, we found that timely vaccination decreased as the age of the children increased, delayed vaccinations (late timeliness) seemed to increase with increasing age, while the proportions of early timeliness showed no clear pattern. This is consistent with a study done in Western Cape, SA which found that there is a direct proportion between vaccine delay and child age, with delay in receipt of subsequent doses [47]. In our study, BCG has the highest proportions of on-time vaccines which could be explained by the fact it is received on the day of delivery at the hospital where it is readily available and hexa4 were the least on-time. MCV2 was the most delayed and there was a long period of delay between MCV2 and hexa4 which could be explained by the fact that as children are growing caregivers are less worried about the health of their children hence paying less attention to vaccine schedules, this is backed up by primary caregiver related reason emerging as the commonest reason for missed vaccinations in our study. Similar observations were also found in studies in the Gambia and Nigeria [63–65].

Vaccine timeliness is a measure of the quality of performance of the EPI in terms of access, affordability, vaccine acceptability and hesitancy [66,67], so it was important to measure it during the COVID-19 pandemic and lock down where the world was on a standstill.
In our study, between the two periods, vaccine timeliness for BCG and hexa1 were the same while PCV3, hexa3, hexa4, and MCV2 timeliness was significantly different. Vaccine doses which were received early for PCV3, hexa3, MCV2 and hexa4 revealed higher percentages in those given pre-pandemic as opposed to those given during the pandemic period. From the caregivers' side, it could happen because in pre-pandemic time they were free to go to the hospital at any time without restrictions hence presenting even when it is not their scheduled time, or children who received vaccines from more than one provider, on HCWs' side it reflects on the knowledge and practices by vaccinators for example not tracking or storing immunisation histories, poor record keeping among others [68]. To our knowledge, no studies were found on the impact of the COVID-19 pandemic on early doses in the child's routine vaccines most concentrated on delayed doses. However, previous studies in Africa have shown a high prevalence of invalid hexa1 and hexa3 doses at median percentages of 12.1% and 5.7% respectively [69]. Surveillance on invalid vaccine doses is important as it warrants

repeat vaccination of doses given earlier than scheduled since there is suboptimal humoral immunity

generated hence suboptimal protection against VPDs [69]. Invalid doses not only have economic implications but also reflect the level of knowledge and practice of the HCWs administering the vaccines.

Our study shows evidence of vaccine delay is more pronounced in the pandemic period than in the pre-pandemic period for doses of PCV3, hexa3, hexa4, and MCV2 which is consistent with more studies done around the world including studies in Saudi Arabia and Pakistan which found delays in the timeliness of routine vaccination during the COVID-19 pandemic [70,71]. These findings could be explained by the fact that, with the COVID-19 pandemic hitting SA harder than other countries in Africa, strict mitigation strategies such as lockdowns were put in place. Lockdown entailed less movement hence caregivers presented to the hospital late when it was safe and the lockdown was less stringent. Fear of COVID-19 by HCWs and caregivers led to closed hospitals or people present later, an overwhelmed health system hence routine health services were affected creating backlogs. Closing of the border and manufacturing of the new COVID-19 vaccine led to vaccine shortages, all of which could lead to delays in vaccine reception. This is consistent with studies in South Africa and other cities where hospitals were noticed to be overwhelmed during the pandemic, for example, in Johannesburg hospitals which had few beds and oxygen available at the beginning of COVID-19 in 2020, a >50% decrease in child healthcare hospital clinics at the beginning of level 5 lockdown in KZN and effect on paediatric vaccine ordering [17,72–74].

Timely vaccines did not have a clear pattern between the two periods. Generally, we would expect people to receive timely vaccinations in the pre-pandemic period than in the pandemic period as most systems were functional.

Age-inappropriate doses in our study applied to BCG, OPV0 and OPV1, rota1 and rota2 but they were observed in all except BCG. The observed doses were significantly different between the pre-COVID-19 and COVID-19 times with higher proportions found in the pandemic period in all four vaccines (OPV0, OPV1, rota1 and rota2). This means that more vaccines were unnecessarily wasted in 2020 than in 2018/19 as children beyond the upper age limit for catch-up vaccination were given vaccination. In a pandemic situation, the consequences of this are debatable as due to bleeding health services, the more children are vaccinated the better therefore the vaccination system is not perfect as it is focusing on quantity

than quality.

In non-pandemic times, doses given beyond their eligibility times (age-inappropriate doses in our study) are important to monitor as they have both economic implications and reflection on the level of knowledge and practice of the HCWs.

Among the 5 multi-dose vaccines, completeness was highest for oral polio vaccines and lowest in the hexavalent vaccine. This could be attributed to the first dose of polio being given at birth where it is readily available at the hospital, assuming most births were hospital births, it could also be because of the oral route of administration and lower number of doses needed contrary to hexavalent which is the first dose is at 6 weeks requiring enormous dedication from caregivers to present at the hospital, it is given in 4 doses and via the intramuscular route risking fear of the pain in their children.

The proportion of missed doses in both periods was similar except for MCV1 and MCV2. While children missed OPV0, OPV1, rota1, hexa1 and hexa2, for the same reasons in the 2 periods, they missed doses of rota2, PCV2, hexa3 and PCV3 for different reasons. For example, primary caregiver and health facility-related reasons were the commonest reasons for missed doses for hexa3 and PCV3 respectively in pre-pandemic while child illness and COVID-19-related reasons were commonest in the pandemic for hexa3 and PCV3 respectively.

The strength of the study is that not only did it analyse individual uptake of childhood vaccines based on detailed timeliness and validity, but it also compared these between two time periods (pandemic and pre-pandemic) making it unique as many studies only analyse coverage or timeliness based on vaccine delay on one time period. This study contributes to vaccine timeliness evidence in the EPI-SA, how and why it is important to look at age-appropriate vaccinations as per recommended schedules to increase the cost-effective running of their vaccination program. This evidence is also important for future policy decisions for instance incorporating vaccine timeliness when assessing indicators of EPI-SA performance. We used data from vaccination cards which are more objective in assessing timeliness than oral recall. The results from the study may be generalisable to populations with similar population parameters as the selected clusters in Soweto for example clusters with high child mortality rates and low SES in urban informal settings.

There is a need to be cautious when interpreting the data because of several imitations. First, the use of secondary data limited the ability to conduct a thorough analysis of the results due to incomplete information, missing data, (> 30%) and changing of variables through the different rounds of data collection which may pose a selection bias especially if the missing data were associated with the outcome (timeliness) or the exposure of interest (pandemic period). Secondly, our findings show crude timeliness associations with the two time periods without looking into other predictors of timeliness. A previous study done in 2012 in Soweto found vaccine shortages, low level of education of the primary caregiver, unknown maternal HIV status, low socioeconomic status, having two or more children < 5 years and HH monthly income <60USD to be predictors of delayed and missed vaccinations [45]. Assuming a constant change in some of these factors over the years, they could change the vaccine timeliness findings observed. Therefore, the COVID-19 pandemic effects observed cannot be concluded as the sole attribution or causal to the difference in vaccine timeliness in the two time periods unless the other predictors are adjusted for. Finally, the data was not corroborated with hospital records which may have dates or other records on reasons for missed doses for instance vaccine stock-outs or closed immunisation centres.

4.1 Implications for practice and research

Grouping vaccine timeliness into Invalid doses/ timely doses/ delayed doses as done in this study is important to ensure effective performance of EPI programs hence correctly attaining individual optimal immunity in children which then can lead to herd immunity, protecting not only individuals but also communities as children are common spreaders of infections. This grouping of timeliness also ensures that there are no missed opportunities for vaccination, hence children with invalid vaccines and missed doses catch up to the required doses. An example would be children who receive invalid vaccine doses which are hardly studied yet have economic implications and reflect the level of knowledge and practices of the HCWs on vaccination administration and the vaccine distribution system. Timeliness is therefore important where policies to improve EPI performance are concerned.

These unique findings call for further research on the prevalence of invalid doses and the knowledge and practices of vaccinators on immunisation practices and other predictors of vaccine timeliness, especially in pandemic times. Vaccine coverage encompasses many aspects for example timeliness and validity of the doses, reflecting the quality of

immunisation

programs. These should also be explored extensively if we are to improve the EPI-SA and vaccination programs worldwide and make progress towards IA2030. Quality routine data with dates is important for decision-making to continuously understand and improve vaccine delivery. Health workers have a big role to play in ensuring the timing of vaccinations by following the guidelines and minimising invalid doses administered to children.

In conclusion, there were more vaccine delays during the pandemic period than in the pre-pandemic period on vaccines received later in childhood. Most early doses were administered in the pre-pandemic time as opposed to the pandemic times. MCV1 missed dose proportions were different between the two time periods with the commonest reasons for missed doses being primary caregiver-related and child-illness. Interventions to improve the timing of vaccines are needed in Soweto to ensure that children are receiving vaccines at the right time (timely) to induce the required immunity to fight VPDs. Children with invalid doses and missed doses need catch-up and SIAs to ensure that all vaccine-eligible children who missed their doses catch up with immunisations. Furthermore, vaccinators should be continuously trained and provided with refresher courses on correct immunisation practices. As we could not explore other predictors of vaccine timeliness, we refrain from attributing the findings to the pandemic alone, therefore we recommend further analytical studies that will consider other factors associated with vaccine timeliness in the COVID-19 time

5 RECOMMENDATIONS

Higher proportions of invalid (early) doses were given in the pre-pandemic time when there was less pressure on health services

Soweto and Thembelihle vaccination centres can improve through, (i) offering vaccination training and monitoring their nursing staff to improve vaccination performance, correct vaccine administration practices and record-keeping to reduce or eliminate (a) early/invalid doses, (b) delayed/late doses.

Higher proportions of late (Delayed) doses given in the pre-pandemic time

(c) Using missed opportunities for vaccination, and (d) false contraindications to vaccination, (ii) improving stock monitoring and developing strategies to resolve supply bottlenecks which may lead to vaccine stock-outs in health facilities if they persist beyond the pandemic period
(iii) organising SIAs to improve vaccine coverage and timeliness after the pandemic has stabilised (iv) organising home-based vaccination outreach programs to reach everyone, especially in a pandemic setting where there are a lot of barriers to EPI services (v) organising effective communication activities to overcome barriers namely vaccine hesitancy and fear of COVID-19 (vi) Ensuring that staff are protected by providing enough materials for infection prevention control, incentives and mental health support so that the staff feel protected and continue offering services. (vii) Training on appropriate HCW behaviour towards the public to avoid deterring people from seeking health services which lead to missed vaccinations.

Missing data in the HDSS

The Soweto HDSS can improve its data quality by (a) updating its data collection strategy, questionnaires and gadgets (b) ensuring that data quality control checks and systems are in place and running for example by using the tablet used for data collection to take a photo of each RTHC, and sending them to the supervisor every day (c) providing continuous frequent training to data collectors, data managers and statisticians. (d) Applying for more funding grants to keep up with increasing data quality needs for example additional data collectors, data managers and biostatisticians to continuously monitor and evaluate the data through data

checks and collection of mistakes as they come. This will decrease the amount of missing data hence making it easier to draw firm conclusions about trends in vaccination coverage and timeliness and the other data collected. It will also decrease the workload that one person has to manage to achieve quality. (e) Setting practical and realistic targets for the data collectors to ensure that they are collecting quality data. (f) Frequent and close monitoring of the data collectors to avoid data fabrication for example by setting strong and independent unanimous data quality team and enforcing existing protocols on those found fabricating data. (g) using software that collates all the data, to easily modify and identify missing data on a real-time basis to motivate follow-up visits that will fill in the missing data. (h) Improving the existing community communication and engagement strategies to increase data completeness by meeting with the community frequently, communicating results found on previously analysed data and providing incentives including health incentives for example offering advice on how to improve their health or health problems observed from previously analysed data, promoting exercise among caregivers, child wellness days in the community and other activities that may benefit the community. These would make the community feel included and cared for and hence improve their participation in the survey. Child wellness days can include weight, height and Mid-Upper Arm Circumference (MUAC) measurements which the study already does. Health and vaccination advice on how to ensure that the child is taken to vaccination visits on time, the direct and indirect benefits of vaccination and addressing some vaccine hesitancy among caregivers. It would have two-fold benefits of improving vaccination coverage and survey participation levels by the community.

The clusters of Soweto and their leaders can improve by (i) organising community-led health coordinated programs to address poor knowledge of immunisation schedules and vaccine hesitancy among caregivers (ii) increasing health facility opening hours to allow everyone to access immunisation services even those who work. (iii) encouraging people to attend community outreach vaccination programs so that people receive scheduled doses timely especially if health facilities are at a distance from their homes. (iv) encouraging community and religious leaders to be advocates of vaccination (v) using mass media programs to increase knowledge of vaccination and its direct and indirect benefits (vi) encouraging caregivers to set a reminder system for child vaccination visit dates. More caregiver initiatives to instil vaccine confidence are needed in Soweto as most reasons for missed vaccination were caregiver driven.

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APPENDICES

Appendix one:

Associations between period and vaccine timeliness coverage for vaccine doses

Vaccine Dose	**Pre-pandemic n (%)**	**Pandemic n (%)**	**P-value**
BCG			
Timely	1,251(96.9)	1,384(96.7)	0.783†
Late	40(3.1)	47(3.3)	
Total	1,291 (100)	1,431(100)	
OPV0			
Timely	1,239(97.0)	1,369 (94.3)	<0.001†
Late	37(2.9)	57(3.9)	
Age-inappropriate	1(0.1)	26(1.8)	
Total	1,277(100)	1,452(100)	
OPV1			
Early	153(14.6)	165(11.5)	0.021†
Timely	849(80.8)	1,202(83.6)	
Late	47(4.5)	59(4.1)	
Age-inappropriate	2(0.2)	12(0.8)	
Total	1,051(100)	1,438(100)	
Hexa1			
Early	137(13.1)	146 (10.0)	0.050†
Timely	857(81.6)	1,231 (84.1)	
Late	56 (5.3)	87 (5.0)	
Total	1,050 (100)	1,464 (100)	
Rota1			
Early	139 (13.2)	141 (9.7)	0.001†
Timely	866 (82.2)	1,251 (85.6)	
Late	47 (4.5)	54 (3.7)	
Age-inappropriate	1 (0.1)	15 (1.0)	
Total	1,053 (100)	1,461 (100)	
PCV1			
Early	137 (13.1)	139 (9.5)	0.016†
Timely	863 (82.4)	1,250 (85.4)	
Late	47 (4.5)	75 (5.1)	
Total	1,047(100)	1,464(100)	
Hexa2			
Early	104 (11.7)	135 (9.3)	0.015†

Late	67 (7.6)	153 (10.5)	
Total	888(100)	1,451(100)	
Hexa3			
Early	86 (11.8)	110 (7.9)	<0.001†
Timely	591(80.7)	1,114 (79.7)	
Late	55 (7.5)	174 (12.5)	
Total	732 (100)	1,398 (100)	
PCV2			
Early	97 (12.9)	117 (8.4)	<0.001
Timely	600 (79.8)	1,111 (79.4)	
Late	55 (7.3)	171 (12.2)	
Total	752(100)	1,399(100)	
Rota2			
Early	115 (15.5)	142 (10.3)	<0.001†
Timely	575 (77.7)	1,080 (78.1)	
Late	49 (6.6)	112 (8.1)	
Age-inappropriate	1 (0.1)	49 (3.5)	
Total	740 (100)	1,383 (100)	
MCV1			
Early	59 (15.3)	141 (10.6)	<0.001†
Timely	308 (79.8)	1,029 (77.3)	
Late	19 (4.9)	162 (12.2)	
Total	386 (100)	1,332 (100)	
PCV3			
Early	39 (32.5)	94 (8.9)	<0.001†
Timely	80 (66.7)	839 (79.6)	
Late	1 (0.8)	121 (11.5)	
Total	120 (100)	1,054 (100)	
MCV2			
Early	11 (100)	67 (8.8)	<0.001*
Timely	0 (0.0)	603 (79.5)	
Late	0 (0.0)	89 (11.7)	
Total	11 (100)	759 (100)	
Hexa4			
Early	3 (100)	39 (17.0)	0.013*
Timely	0 (0.0)	177 (77.3)	
Late	0 (0.0)	13 (5.7)	
Total	3 (100)	229 (100)	
Timely	717 (80.7)	1,163(80.2)	

Appendix two-Plagiarism form

SCHOOL OF PUBLIC HEALTH

STUDENT DECLARATION

PLAGIARISM

I, Chikondi Charity Kandulu (student number (2380761) am a post-graduate student registered for the degree/program MMED Vaccinology at the Wits School of Public Health.

I am submitting written work for the MSc research report for the topic IMPACT OF THE COVID-19 PANDEMIC ON ACCESS TO ROUTINE IMMUNISATION

I hereby declare the following:

- I am aware that plagiarism is the use of someone else's work without their permission and/or without acknowledging the source.

- I am aware that plagiarism is wrong
- I confirm that the work submitted for the above course and module, is my work, except where I have stated otherwise
- I have followed the required conventions in referencing the thoughts and ideas of others
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my unaided work or if I have failed to acknowledge the ideas or writing.

Signature:_____ Date: 29 MAR 2022

Appendix three: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr CC Kandulu
School of Pathology
Wits Vaccines & Infectious Diseases Analytics RU
Medical School
University

E-mail: 2380761@students.wits.ac.za

CC: Supervisor: Drs C Cutland, R Biellik and P Mutevedzi
<Clare.Cutland@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2021/09/13

REF: R14/49

PROTOCOL NO: **M210630** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Impact of the COVID-19 pandemic on access to routine immunisation*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Appendix four: Approved protocol