Descriptive analysis of routine childhood immunisation timeliness in the Western Cape, South Africa

By

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Submitted to the University of Cape Town in partial fulfilment of the requirements for the degree of **Master of Public Health (Epidemiology and Biostatistics)**

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(24 August 2021)

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Declaration

I, Ntombifuthi Blose (BLSNTO004), hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in the University of Cape Town (UCT) or any other university.

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Abstract

Background:

Adherence to the recommended age-specific immunisation schedules is critical in ensuring vaccine effectiveness against vaccine preventable diseases (VPDs). Delays in the uptake of routine childhood immunisations lead to an increase in children susceptible to VPDs. Catch-up vaccination campaigns are strategies aimed at minimising the time at risk of VPDs and alleviating missed immunisation opportunities. However, there is limited data on immunisation timeliness in the Western Cape to contribute to developing effective catch-up vaccination campaigns. Therefore, this study sought to assess the timeliness of age-specific routine childhood immunisation within the Western Cape province of South Africa.

Methods:

We reviewed 709 participant records from a prospective health-facility based study conducted between 2012 and 2016 in Cape Town, South Africa. The primary outcome of interest was receiving age-specific immunisations ≥ 4 weeks (28 days) of that recommended for age as per the South African Expanded Programme on Immunisation (EPI) schedule. Using secondary data, the prevalence of delayed uptake of immunisations and time-at-risk for each vaccine was determined using proportions and medians and interquartile range (IQR). Multivariable logistic regression ($p<0.05$) was used to determine the association between potential socio-economic risk factors and delayed uptake of routine childhood immunisations.

Results:

A total of 652/709 (91.9%) participants with a median age of 11 [IQR 4.5 – 28.0] months were eligible for analysis in this study. A trend of decreasing immunisation coverage with increasing age was observed among study participants. Notably, a trend of increasing delay in the uptake of routine vaccines and an increasing median time-at-risk of VPDs in age-specific immunisations was observed with increasing age. The highest delay in the uptake of vaccine doses was observed among the 3rd dose

of the DTP3 vaccine 163 (34.6%), while the lowest was seen among the birth doses [(BCG – 40 (6.5%) and OPV – 43 (7%)]. The longest median time-at-risk of VPDs, was with the 2nd dose of the measles vaccine dose [12.9 (IQRs 6.7-38.6) weeks] and the lowest was OPV birth dose [6.3 (5.3-9.1) weeks]. Multivariable logistic regression analysis showed that participants who attended pre-school or creche compared to those who did not, were protected against delaying uptake of the 3rd dose of the Hepatitis B vaccine and 2nd dose of the measles vaccine. While those who had adult caregivers compared to those who had adolescent caregivers, were protected against delaying the uptake of the 1st rotavirus vaccine dose. Participants from households of low and upper-middle socio-economic IQR compared to high socio-economic status (SES) based on SES scores calculated from household data (i.e., availability and sources of amenities such as water, fuel, toilets, and level of maternal education) were more likely to delay uptake of the 3rd does of the Pneumococcal Conjugate Vaccine and the 1st dose of the measles vaccine, respectively.

Conclusion:

Using DTP3 coverage as proxy for national immunisation coverage, immunisation coverage in this population fell below the recommended 95% immunisation coverage rate. Additional population delays in the uptake of vaccine doses increases the time during which infants and children are susceptible to potential fatal VPDs. The observed increase in delayed immunisation and increased time-at-risk of VPDs, calls for an urgent need to address timing of vaccination particularly in late infancy and in the second year of life. There is an urgent need to develop strategies aimed at mitigating factors associated with delay in uptake of routine childhood vaccines in the Western Cape Province. Since creche attendance conferred protection against the delay in uptake of vaccines, mitigation strategies implemented upstream by the department of basic education, as well as health and immunisation service providers should strengthen collaborations to ensure that timely vaccine uptake among creche attendees is regularly monitored. Where delays are identified, catch-up strategies can be implemented at educational facilities or referrals to immunization clinics. It is important that this strategy is coupled with caregiver and healthcare worker vaccine education on the importance of timely immunisation uptake. Education about timely vaccine uptake will aid in the provision of informed council from healthcare providers

to – not only adult caregivers - but adolescent caregivers as well, with the aim to reduce delayed uptake of vaccine amongst those raised by adolescent caregiver. The health system and the Expanded Programme of Immunisation on South Africa (EPI-SA) should couple these interventions with effective mobile reminder systems. These reminder systems will particularly serve the purpose to remind those caregivers whose delay uptake of vaccines as a result of a busy schedule. This could improve adherence to the recommended childhood immunisation schedule. Generally, for such interventions to work, effective monitoring and surveillance of immunisation services and vaccines is critical in achieving a high immunisation coverage and timely uptake of vaccines. Future studies should continuously monitor immunisation coverage and timeliness data in the Western Cape Province and South Africa as a whole to support evidence-based strengthening of provincial and national immunisation services.

Acknowledgments

I would like to thank the team at the Vaccines for Africa Initiative (VACFA); Prof. Gregory Hussey, Dr Benjamin Kagina, Dr Edina Amponsah-Dacosta and Prof. Rudzani Muloiwa for hosting me during my research project. To Dr Benjamin Kagina, Dr Edina Amponsah-Dacosta and Prof. Rudzani Muloiwa, thank you for introducing me to Public Health and for the continuous support and supervision of my dissertation write-up.

I can never thank VACFA enough for the exposure and training in vaccinology and public health, that they have made available to me. Dr Edina, in addition to supervision, thank you for helping me with administrative requirements of my research and the many scholarship applications. But most importantly thank you for helping me contextualise my research project. Prof. Rudzani, thank you for assisting me with contextualising the epidemiological and statistical component of my research project. I would like to also thank Mr Stanford Flanagan for our random, refreshing, and lengthy life conversations at the VACFA office after a hectic day of course work.

I would like to further extend my gratitude to VACFA for the financial support throughout my MPH degree.

To Mr Elton Mukonda and Mr Luke Hannan from the School of Public Health and Family Medicine, University of Cape Town (UCT), I am grateful for your assistance with R code for the cleaning of my massive dataset. To Miss Kamunkhwala Gausi, from the Division of Clinical Pharmacology, Department of Medicine UCT; having a housemate who is a Statistician by training really came in handy, thank you for the late nights.

To the Blose family, you guys are just great. I would like to thank my parents, Mr April Blose and Mrs Juliet Blose for continually supporting my career choices. I am forever grateful. To my one and only sister, Miss Lungile Blose, *dude,* thank you for keeping me sane, and most importantly, thank you for taking on the ‘deputy’ parent role for my daughter when I was away. Last, but definitely not least; to my babies, Yamukelwa Blose and Lubanzi Blose, I know you are only 6 and 4 years old, but when you are old

enough to read this, I want you to use this acknowledgment as motivation to study and chase your dreams just like how I have achieved and went beyond my dream of becoming a scientist.

Lastly, I would like to express my gratitude to the Department of Science and Technology/Department of Science and Innovation and The Council for Scientific and Industrial Research Inter-bursary Support programme for funding my MPH degree from 2019 to 2020.

List of Abbreviations

BCG	Bacillus Calmette–Guerin
CRF	Case Report Form
DTP-IPV-HiB (DTP)	Diphtheria Tetanus Pertussis- Inactivated Poliomyelitis Vaccine-Haemophilus Influenzae type B
EPI-SA	South African Expanded Programme on Immunisation
LMICs	Low- and Middle- Income Countries
OPV	Oral Polio Vaccine
PCV	Pneumococcal Conjugate Vaccine
RV	Rotavirus Vaccine
RTHC	Road to Health Card
SA	South Africa
UNICEF	United Nations Children's Emergency Fund
VPD	Vaccine Preventable Diseases
WCED	Western Cape Department of Education
WHO	World Health Organisation

Thesis Organization

This thesis is divided into three sections: Part A to Part C.

Part A details the research protocol which includes a background to the study, the study rationale, aim and objectives, methods, and ethical considerations.

The findings of the study are presented in a journal-ready manuscript format in Part B. This manuscript has been formatted according to the author submission guidelines of the targeted journal, *Vaccine* (*see Appendix 4)*. In Part B, the findings, strengths, and limitations of the study are discussed in detail in the context of relevant published literature on vaccine timeliness. In addition, relevant conclusions and recommendations are presented here.

Lastly, all supplementary materials relevant to the study are provided as an appendix section in Part C. These supplementary materials include supporting data and analyses, the ethics clearance certificate to conduct this study and *Vaccine* journal submission guidelines. The *Vaccine* referencing style has been used throughout this thesis in accordance with the author submission guidelines.

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PART A: PROTOCOL

Descriptive analysis of routine childhood immunisation timeliness in the Western Cape, South Africa

Introduction

Immunisation is universally accepted as the single most cost-effective public health intervention against morbidity, disability and mortality caused by vaccine preventable diseases (VPDs). In 2019, the World Health Organisation (WHO) estimated routine childhood immunisation programs to have reached 116.2 million (85%) children worldwide, saving millions of lives [1]. In South Africa (SA), immunisation is estimated to avert about 2.5 million deaths annually [2]. The national coverage among South African children who received the primary course of routine immunisation before the age of 1 year was reported to be 77% in 2017/2018, with the Western Cape Province being one of the provinces to exceed this national average [3]. According to the South African Expanded Programme of Immunisation (EPI-SA) schedule, children should receive seventeen vaccine doses from birth to 12 years [4]. Despite the provision of free routine immunisation services through EPI-SA, outbreaks of VPDs continue to be a public health challenge in the country [5]. In 2017, a measles and rubella outbreak survey identified cases of measles and rubella in Kwa-Zulu Natal, Gauteng, and the Western Cape Provinces. Additionally, a report by the National Institute for Communicable Diseases documented increased cases of pertussis in the Western Cape Province between October 2017 to January 2018 [6].

The reported cases and outbreaks of VPDs in South Africa could be attributed to sub-optimal uptake of routine childhood vaccines. Challenges associated with vaccine coverage are multi-pronged and include broader health systems constraints (e.g. vaccine stock-outs, challenges in vaccine delivery), as well as contextual (e.g. socio-economic factors) and individual (e.g. vaccine hesitancy) factors [5]. To achieve full immunisation coverage and to prevent missed or delayed immunisations, challenges with vaccine coverage must be clearly defined.

Delayed and missed immunisations are associated with inadequate development of immune protection, which predisposes to the acquisition of VPDs [7]. To achieve maximal protection against VPDs, children need to receive all immunisations within the recommended intervals and at the recommended age [7]. The concept of receiving immunisations as per recommended EPI schedule is referred to as vaccine timeliness, and may be defined as a) the receipt of vaccines at recommended ages and intervals, b) the interval, accessibility and the specificity of the vaccine, c) up-to-date immunisation at a certain threshold age, and d) immunisation administered within a certain time in relation to the recommended age for immunisation [7-9]. In general, delayed immunisation is defined in the published literature as any deviation of ≥4 weeks from the recommended EPI schedule [10-15]. There is currently no consensus in the published literature from low- and middle- income countries (LMICs) on the definition of delayed immunisation or immunisation timeliness. The lack of a standard definition of timeliness as an immunisation coverage indicator, is due to the variation in the immunisation schedules globally [16]. An unclear definition of vaccine timeliness makes the elucidation of timing-related challenges to immunisation complex. Therefore, alternative services catering for children and adults who have missed or have not completed routine immunisation are vital.

Catch-up vaccination programs are strategies established to protect individuals who missed or delayed routine immunisation [17]. These strategies have been shown to be successful in the control of VPDs in LMICs, including areas of political conflict [18]. The EPI-SA catch-up vaccination guidelines caters for the administration of vaccine doses for children who missed previous doses, and for adults who have high risk for diseases [18]. Essentially, effective catch-up vaccination programs should be informed by evidence on vaccine timeliness. Unfortunately, such evidence from South Africa is currently scarce.

Problem statement

Successful immunisation programs require a well-functioning health system with adherent individuals in order to achieve age-specific, full immunisation coverage and effective control of VPDs. Delays in vaccine timeliness, and challenges in the broader health system such as vaccine stock-outs, could potentially compromise efforts towards the control of VPDs. In the Western Cape Province of SA, there have been reports of outbreaks of VPDs such as measles, rubella, and pertussis. These outbreaks have been reported in all populations, mainly in children who had potentially missed routine immunisation during infancy. The observed outbreaks of VPDs could be attributed to sub-optimal immunisation coverage. Given that routine infant immunisation is provided free of charge through EPI-SA, it is important to characterise vaccine timeliness in the Western Cape Province and to explore the increase in time-at-risk for VPDs due to lack of timely immunisations.

Research Question

This study seeks to address the following research questions:

a) What is the level of delay to timely, age-specific immunisation among children presenting with respiratory illness to public health facilities in the City of Cape Town, South Africa?
b) What is the duration of time between expected age of immunisation and the time children actually receive vaccines in the City of Cape Town?

Aim

To assess the delay in timeliness of age-specific routine immunisation in children presenting with respiratory tract infections in the City of Cape Town, Western Cape Province, South Africa.

Objectives

a) To conduct a descriptive evaluation of the timeliness of age-specific routine immunisation among a health facility-based population of children in the City of Cape Town, Western Cape Province.
b) To describe the degree of delayed age-specific routine immunisation among children who were identified to have not received age-specific immunisations on time.
c) To describe and compare the socio-demographic and economic risk factors associated with age-specific immunisation timeliness between the children who received immunisations on time and those who delayed or missed immunisations.

Methods

a) Study design

This study will involve a retrospective analysis of data collected during a parent prospective study that was conducted between 2012 and 2016. The study investigated the incidence and risk factors for pertussis in South African children less than 13 years of age. These children presented with mild to severe respiratory tract infections at health facilities (i.e. Red Cross War Memorial Hospital, Mitchells Plain District Hospital, Eastridge Clinic, Athlone - Silvertown Clinic and Life Vincent Pallotti Hospital) within the City of Cape Town in the Western Cape Province of South Africa [19].

b) Sample size

Up to 709 participant data is available for this secondary analysis. An estimated minimum of 500 children's records are expected to fulfil the inclusion criteria, with an

estimated proportion of 88% (85.2%;90.8%) of timely immunisations and 12% (9.2%;14.8%) delayed immunisations [15]. Other possible precision values based on different estimates of proportions and sample sizes are presented in Table 1.

Table 1: Proportions of delayed immunisation at varying sample sizes

	Proportion of children delayed in receiving timely immunisations			
Number enrolled	**50%**	**40%**	**30%**	**20%**
400	45.1%; 54.9%	35.2%; 44,8%	25.5%; 34.5%	16.1%;23.9%
500	45.6%;54.4%	35.7%; 44.3%	26.0%; 34.0%	16.5%; 23.5%
600	46.0%;54.0%	36.1%; 43.9%	26.3%; 33.7%	16.8%; 23.2%
700	46.3%;53.7%	36.4%; 43.6%	26.6%; 33.4%	17.0%; 23.0%

Sample size, proportions and precision estimates were calculated using the following formula:

$n = \frac{p(1-p)(1.96)^2}{d^2}$, Where *p* is the expected proportion and *d* is the precision.

c) Inclusion and exclusion criteria

Data will only be retrieved for participants if the following criteria are met:

- Availability of immunisation history based on full age-specific immunisation data from Road to Health Cards[1] (RTHC)
- Availability of Case Report Forms[2] (CRF) with clinical, socio- demographic and economic data

Data for participants who do not meet the inclusion criteria will be excluded from further analysis.

[1] A template of the South African Road to Health Card (RTHC) is provided as part of the Case Report Form in Appendix 2

[2] A template of the Case Report Form (CRF) used in data collection is provided in Appendix 1

d) Data collection

The population studied as part of the parent study presents a unique opportunity to retrospectively investigate vaccine timeliness among children in the City of Cape Town, Western Cape. A total of 709 children between the ages of 26 days and 13 years were enrolled into the parent study. As indicated previously, data on immunisation history in the form of RTHCs, as well as socio-demographic and economic data of mothers or caregivers were recorded from CRFs into a research database. The current study will make use of this secondary dataset. Variables such as immunisation history, socio- demographic and economic data (e.g., participant age, care-giver socioeconomic quartiles, care-giver education levels) will be retrieved from this parent research database Table 2.

Table 2: Variables extracted from case report forms

	Type	Scale	Categories/units
Participant demographics			
Age	Numerical	Continuous	Months
Sex	Categorical	Binary	Male, Female
Race	Categorical	Polytomous	Black, Coloured, Other[α]
Creche[β]	Categorical	Polytomous	Yes, no, unknown
Caregiver demographics			
Age	Numerical	Continuous	Years
	Categorical	Binary	Adult, adolescent
Highest grade	Numerical	Continuous	Grade
Education	Categorical	Polytomous	Basic, higher, no school, unknown
Socio-economic quartiles	Categorical	Polytomous	Low, low-middle, upper-middle, high

[α]Other – Asian/Indian or white

[β]Preschool, Kindergarten

e) Outcomes of interests

The primary outcome of interest will be equivalent to a Yes/No answer to the question, "Did the child receive age-specific immunisations in time?" An outcome of 'Yes' would be taken as a child who received the vaccine doses ≤4 days before or within 4 weeks (28 days) of that recommended for age as per the EPI-SA schedule. 'No' would be taken as not having received age specific vaccines or receiving vaccines ≥4 weeks after the recommended schedule [20] .

Although the outcome of interest is delay, proportions (in percentages) of children who received doses for ages earlier than recommended will also be described.

f) Data analysis

Demographic characteristics and baseline clinical findings extracted from CRFs and RTHCs will be tabulated to provide a background description of the study population. Continuous numerical data will be described using means/medians and standard

deviations/interquartile ranges depending on the distribution. Proportions will be depicted as percentages with 95% confidence intervals to describe categorical variables. T-tests will be used to analyse the difference in means between continuous normally distributed variables. Differences in medians for non-normally continuous data will be described using Mann-Whitney-U tests. Categorical variable associations will be determined using Chi-squared/ Fishers-exact tests as appropriate.

To evaluate timeliness, proportions (as percentages) of children receiving and not receiving age-specific immunisations at the recommended time will be described for each vaccine at each age timepoint. The evaluation will be done from participants who are eligible (i.e., participants who meet the age requirement to receive vaccines at specific timepoints). Timeliness of vaccine uptake will be calculated as the difference in the expected date and the actual date of receipt of the age-specific immunisation. Duration of delay in uptake of the vaccines will be described for those who did not receive timely immunisations.

All statistical analyses will be conducted using R version 3.5.1 (2018-07-02) and R studio version 1.3.1073. Where hypothesis testing has been done, significance level will be set at a two-tailed $P<0.05$ [21].

g) Risks and benefits

This descriptive study is a low-risk study as it will only make use of secondary data and will not require the direct participation of any individuals. The results of this study will in no way be a potential source of harm or distress.

Participants of the parent study will not have direct benefits from the conduct of this study. However, the Western Cape Department of Health and the EPI-SA will benefit from the anticipated findings of the study as the evidence generated will contribute to informing strategies aimed at improving vaccine timeliness and routine immunisation services in South Africa.

h) Study limitations

This study will make use of a health facility-based population who may have characteristics that are different from the general population. In addition to this, the geographical focus of the study will be restricted to the Western Cape Province. As a result, the representativeness of the study population and the generalizability of the evidence generated may be limited. Therefore, the findings of this study will have to be interpreted with caution. Missing and incomplete data from existing records have been found to introduce inaccuracy in secondary studies [24]. Information bias due to incorrect documentation of the date of administration of immunisation by health workers, will be reduced by verifying whether the dates recorded as receipt of immunisation are consistent with the date, we expect a child to receive age-specific immunisations according to EPI-SA. Missing data from CRFs and RTHCs from the parent study will be excluded. Only complete cases will be used in the analysis.

i) Privacy and confidentiality

To ensure the confidentiality of all participants, unique participant identification numbers will be assigned to each participant. Participant data will be stored and backed-up in a database accessible to the primary researcher, and the supervisors (Dr Edina Amponsah-Dacosta, Professor Rudzani Muloiwa, and Dr Benjamin Kagina) linked to this study.

j) Dissemination

This study is intended for an MPH dissertation, where one of the expected outcomes is a peer reviewed publication. Findings of this proposed study are expected to be published in one of the vaccinology, epidemiology, or paediatrics journals. Additionally, study findings will be presented at conferences and workshops, including the Vaccines

for Africa Initiative's Annual African Vaccinology Course which is attended by various stakeholders involved in vaccinology programs across Africa.

Study timeline

Table 3: The anticipated timeline for the study

	2019			2020			2021
Activities	**Jun-Aug**	**Sep-Nov**	**Dec**	**Jan-Mar**	**Apr-Jun**	**Jul-Dec**	**Jan-Mar**
Protocol writing	X	X	X				
Submission to DRC* and HREC*		X	X	X			
Data extraction and analysis			X	X	X		
Manuscript write-up					X	X	X
Mini-dissertation submission							X

**DRC – Departmental Research Committee; HREC – Human Research Ethics Committee*

Expected significance of the study.

This study aims to provide a descriptive analysis of delayed immunisation, the socio-demographic and economic risk factors associated with or delayed routine immunisation. Our findings could be used to explore ways to strengthen childhood immunisation in the Western Cape Province by informing strategies to improve timely uptake of routine vaccines.

Ethical approval

The parent study on which this study builds was approved by the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences, University of Cape Town, South Africa (reference: 371/2011). Given that this study will make use of secondary data, formal ethics approval will not be required. However, clearance to conduct this study as part of the primary researcher's MPH degree, will be requested from the School of Public Health and Family Medicine, Departmental Research Committee (DRC) and HREC.

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PART B: Journal Manuscript

Descriptive analysis of routine childhood immunisation timeliness in the Western Cape, South Africa

Targeted Journal: Vaccine

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Abstract

Adherence to the recommended age-specific immunisation schedules is critical in ensuring vaccine effectiveness against vaccine preventable diseases (VPDs). There is limited data on immunisation timeliness in Sub-Saharan Africa. Therefore, this study assessed the timeliness of age-specific routine childhood immunisation within the Western Cape Province (WCP) of South Africa (SA).

Participant records (N=709) from a prospective health-facility based study conducted in Cape Town, SA in 2012-2016 were analysed. The outcome was receiving age-specific immunisations ≥ 4 weeks of that recommended for age as per the South African Expanded Programme on Immunisation (EPI-SA) schedule. Proportions, medians (IQR) and regression were used to obtain the prevalence, time-at-risk, and risk factors for delayed immunisation uptake.

A total of 652/709 (91.9%) participants were eligible. Immunisation coverage declined with age from 94.9% (95% CI 92.9-96.4) at birth to 72.0% (95% CI 65.7-77.6) at 18 months. The highest delay in the uptake of vaccine doses was observed among the 3rd dose of the DTP vaccine [163 (34.6% (95% CI 30.3-39.1)], while the lowest was seen among BCG [40 (6.5% (95% CI 4.7-8.8)]. The longest median time-at-risk of VPDs, was among the 2nd dose of the measles vaccine dose [12.9 (IQR 6.7-38.6) weeks] and the lowest was OPV birth dose [IQR 6.3 (5.3-9.1) weeks]. Having an adolescent caregiver, low and upper-middle socio-economic quartiles was associated with delayed uptake of doses.

Delayed vaccination increases the time of susceptibility to VPDs during infancy and childhood. There is a need to develop strategies aimed at mitigating factors associated with delay in uptake of routine childhood vaccines in the WCP. Mitigation strategies should provide vaccine education and mobile reminder systems. Education about timely vaccine uptake will aid in the provision of informed council from healthcare providers to caregivers. Mobile reminder would remind caregivers with busy schedules.

Keywords:

Childhood immunisation, Vaccine, Vaccine adherence, Vaccine coverage, Vaccine preventable diseases, South Africa

Highlights

- Immunisation coverage has an inverse relationship with age, while delay in vaccine uptake has a direct relationship with age.
- High vaccine coverage rates do not translate to timely receipt of routine childhood vaccines.
- Time-at-risk for vaccine preventable diseases is positively associated with increasing immunisation age timepoints.
- Preschool attendance and having adult caregivers are protective against delaying vaccine uptake.
- Low and upper-middle socio-economic IQR is harmful towards delayed uptake of routine vaccines

Introduction

The World Health Organisation (WHO) first recommended the administration of routine childhood vaccines through the Expanded Programme on Immunisation (EPI) in 1974. Four decades on, this initiative has proven to be the most cost-effective public health strategy globally, reducing childhood morbidity, disability and death associated with vaccine preventable diseases (VPDs) [1–4]. In 2019, the global immunisation coverage with the third dose of the diphtheria, tetanus, and pertussis vaccine (DTP-3) was 85%, with less than 19.7 million children (<20%) deemed susceptible to VPDs [5]. Data received as of October 2020, show DTP-3 coverage to be 74% in Africa [6]. These figures are concerning as in 2019, WHO estimated that 5.2 million children under 5 years old had died from preventable diseases, including VPDs. Additionally, sub-Saharan Africa accounts for the highest number of preventable deaths (including VPDs) with 1 in 13 children dying before their fifth birthday [7].

In South Africa, routine childhood immunisation is reported to avert an estimated 2.5 million deaths annually [8]. The immunisation coverage for fully vaccinated under 1 year olds in 2017/8 was 77% [8].The Western Cape, Mpumalanga, Northern Cape, and Kwa-Zulu Natal provinces exceeded this national average [5]. In contrast, using the first measles dose as a proxy for under 1 year vaccine coverage, estimations by the WHO and the United Nations Children's' Fund (UNICEF) as of June 2020, show that immunisation coverage in South Africa has increased by only 2% from the previous report in 2017/8 [9]. As effective as vaccines have been proven to be, these low immunisation coverage figures in South Africa show that despite the provision of free vaccines, the efforts of the South African Expanded Programme on Immunisation (EPI-SA) by the South African Health System and government can potentially be undermined.

Outbreaks of VPDs such as measles and rubella in Gauteng, Kwa-Zulu Natal and the Western Cape provinces have been reported as recent as 2017 [10]. Additionally, cases of pertussis in the Western Cape were reported between October 2017 to January 2018 [11]. While these outbreaks are a cause for concern given that VPDs have the potential to cause serious morbidity and mortality, they also suggest that there might be an underlying problem since these outbreaks were documented in

provinces that exceeded the national immunisation coverage rate [12,13]. An improved understanding of the underlying determinants of outbreaks of VPDs despite optimal vaccination coverage rates could help inform evidence-based interventions.

Immunisation coverage is defined as the proportion of people who receive vaccines at a certain age, regardless of the timing of administration [14]. While widely used to measure the performance of immunisation programs, immunisation coverage has its limitations [14,15]. This is because, immunisation coverage alone cannot inform on the level of adherence to the EPI schedule. For example, a study conducted using data from Soweto (Gauteng) and Pietermaritzburg (Kwa-Zulu Natal), in South Africa, found immunisation coverage at the sites to be 93.9% and 90.6% respectively. Despite this, it was also reported that 32.2% and 25.2% of the study participants delayed vaccine uptake respectively [16]. There is currently no consensus for how immunisation timeliness should be defined. However, previous studies conducted in low- and middle- income (LMIC) settings have described immunisation timeliness to be a) the receipt of vaccines at recommended ages and intervals, b) the interval, accessibility and the specificity of the vaccine, c) the up-to-date immunisation at a certain threshold, and d) immunisation administration within a certain time in relation to the recommended age for immunisation [14,17,18]. Evidently, timeliness is not synonymous with coverage, but instead the two measures can be used together to get a population estimate for immunisation timing and coverage [14]. This distinction is important more so because lack of immunisation timeliness can potential be a barrier to full immunisation coverage.

Immunisation coverage is related to the receipt or non-receipt of immunisations. While immunisation timeliness addresses the analytical questions such as whether immunisations were received on time, early, or delayed. Delays in immunisations are associated with inadequate developments of immune protection, which predisposes to the acquisition of VPDs [17]. The lack of a standard definition of delayed immunisation contributes to the complexity of quantifying delay and determining reasons for delay [18]. Despite the lack of a standard definition, generally delay in immunisations based on studies conducted in LMICs, has been described as ≥4 weeks (28 days) deviation from the EPI schedule [20-23].

To mitigate the potential detrimental impact of delayed uptake of routine childhood vaccines, catch up immunisations are necessary to protect populations who missed or delayed immunisations. These strategies not only give individuals another chance of protection from VPDs, but population-based catch-up strategies can also reach areas of political conflict [24]. Essentially, effective catch-up vaccination programs should be informed by evidence on vaccine timeliness. Unfortunately, such evidence from South Africa is currently scarce.

This study sought to assess the delay in timeliness of age-specific routine immunisation in children presenting with respiratory tract infections in the City of Cape Town, Western Cape Province, South Africa. Primarily, the study set to describe the proportion of children with delayed timeliness of age-specific routine immunisation and to describe the degree of this delay. As a secondary outcome, the study intended to investigate for risk factors that lead to children not receiving age-specific immunisations on time.

Methods

Study design

This study involved a retrospective analysis of data collected during a parent prospective study that was conducted between 2012 and 2016. The study investigated the incidence and risk factors for pertussis in South African children less than 13 years of age. The children presented to four health facilities (i.e. Red Cross War Memorial Hospital, Mitchells Plain Day Hospital, Eastridge Clinic and Athlone - Silvertown Clinic) with mild to severe respiratory tract infections [25].

The study included all participants from the original database for whom immunisation information as noted in the handheld immunisation record, the Road to Health Card

(RTHC) was available. The information had to include the date each dose of the vaccine was received. In addition, the participants Case Report Forms (CRFs) had to contain sufficient data to assess for potential risk factors.

Variables such as immunisation history, socio- demographic and economic data (e.g., participant age, care-giver socioeconomic status, care-giver education levels) were retrieved from the research database. Socio-economic status was categorized into IQRs on the basis of a validated weighted composite score that included asset ownership, employment, and education [26].

Definitions

Eligibility at each time point was described as participants who were old enough to receive vaccines as recommended. Up to date was described as receiving all the recommended vaccines at the recommended age time points. On-time uptake of vaccines was described as vaccine doses received less than 5 days before and not longer than 28 days after the recommended age as per the EPI-SA schedule [14]. Early uptake of vaccine doses was defined as anything received earlier than 4 days before the recommended age [14]. Delayed uptake of vaccine dose was defined as receiving vaccines more than 28 days after the recommended schedule age [27].

Data analysis

Demographic characteristics and baseline clinical findings extracted from CRFs and RTHCs were tabulated to provide a background description of the study population. Continuous numerical data were described using medians and interquartile ranges (IQR). Proportions were depicted as percentages to describe categorical variables. Differences in distribution of continuous data were assessed using Mann-Whitney-U tests. Associations between two categorical variables were assessed using Chi-square or Fisher’s exact tests as appropriate.

The primary outcome of interest was the receipt of a vaccine dose later than 28 days of that recommended for age as per the EPI-SA schedule (birth doses are no exception). To evaluate timeliness, proportions of participants receiving and not receiving age-specific immunisations, at the recommended time were described for each vaccine. Timeliness in immunisation was calculated as the difference in the expected date and the actual date of receipt of the age-specific immunisation. Duration of delay was described for those who did not receive timely immunisations.

The BCG birth dose was used as a reference to compare the median duration in delays with age. BCG is expected to have the lowest delay in uptake, and therefore when used as a reference, presents an opportunity to depict trends (increase/decrease) for delays with age.

Factors associated with delayed immunisation for each vaccine was evaluated using logistic regression using the binary outcome of Yes/ No (Delayed/On time). All statistical analyses were conducted using R version 3.5.1 (2018-07-02) and R studio version 1.3.1073. Where hypothesis testing was done, significance level was set at a two-tailed $P<0.05$ [28].

We estimated that a minimum of 500 children's records of the original database would meet the criteria inclusion. This would give a sample size sufficient to give precisions within 5% of all possible estimates of the primary outcome between 20% and 50%, which we deemed to be acceptable.

The study was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee [HREC 027/2020].

Results

Demographic characteristics of the study population

A total of 652 (92%) participants of the original database of 709 children had sufficient data for analysis. Figure 1. The median age of the included children was 11 [IQR 4.5 - 28.0] months.

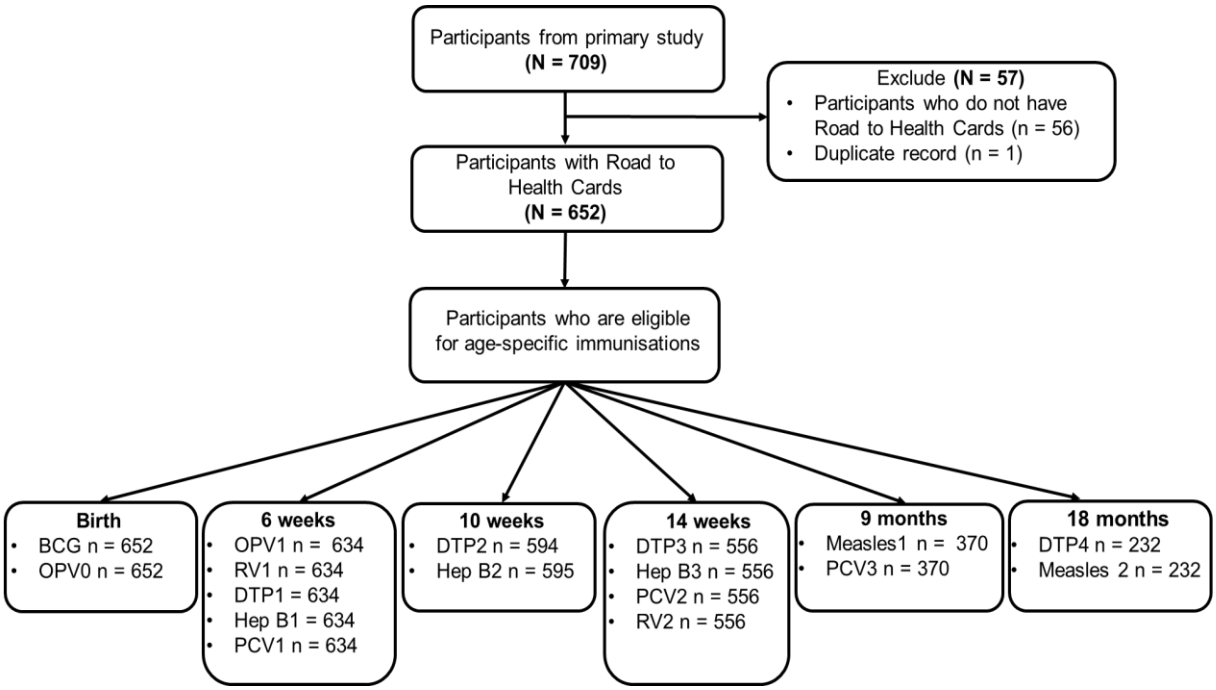

Figure 1: Flow diagram of participants included in the study. BCG – Bacillus Calmette-Guérin, OPV0 – birth dose Oral polio vaccine, OPV1 – 1st dose Oral polio vaccine, RV1 – 1st dose Rotavirus, DTP1 – 1st dose Diphtheria/Tetanus, Pertussis, Inactivated Poliomyelitis vaccine and Haemophilus Influenzae Type B (DTP/IPV/HiB), Hep B1 – 1st dose Hepatitis B, PCV1 – 1st dose Pneumococcal Conjugate vaccine, DTP2 - 2nd dose DTP/IPV/HiB, Hep B2 – 2nd dose Hepatitis B, DTP3 - 3rd dose DTP/IPV/HiB, Hep B3 – 3rd dose Hepatitis B, PCV2 – 2nd dose Pneumococcal vaccine, RV2 – 2nd dose Rotavirus, Measles 1 – 1st dose Measles, PCV3 – 3rd dose Pneumococcal vaccine, DTP4 - 4th dose DTP/IPV/HiB, Measles 2 – 2nd dose Measles

Most of the participants were male with 360 (55.2%). Of the total 605 participants who were eligible to attend creche 457 (75.5%) did not attend. Of the available 642 records, in which participants divulged their racial background 389 (60.6%) identified as Black, 247 (38.5%) as Coloured (mixed ancestry) and 6/642 (0.9%) as other races. In 639 (98%) the caregivers were mothers, with a median age of 28 [IQR 24 - 34] years. The caregivers reported having attained a basic level of education in 622 (95.4%) instances with grade 11 [IQR 10 - 12] being the median highest grade reached within the study population. Other demographic characteristics are shown in Table 1.

Table 1: Participant and caregiver baseline characteristics (N = 652)

Characteristic	n (%)
Participant demographics	
Sex (n= 652)	
Female	292 (44.8)
Male	360 (55.2)
Race (n=642) α	
Black	389 (60.6)
Coloured/Mixed ancestry	247 (38.5)
Other	6 (0.9)
Creche ¥ (n=605) α	
No	457 (75.5)
Yes	145 (24.0)
Unknown	3 (0.5)
Caregiver demographics	
Relationship with child (n=652)	
Mother	639 (98.0)
Other	13 (2.0)
Education (n= 625) α	
Higher education	21 (3.2)
Basic education	622 (95.4)
No school	1 (0.2)
Unknown	8 (1.2)
Socio-economic IQR (n=547) α	
Low	129 (23.6)
Lower-middle	53 (9.7)
Upper-middle	285 (52.1)
High	80 (14.6)

α – Missing data; ¥ – Preschool, Kindergarten, Nursery

Table 2: Immunisation coverage and delay and duration time at risk of Vaccine Preventable Diseases

Timepoints	Immunisation	Eligible n (%)	Coverage n (%)	Delay in weeks Median [IQR]
Birth	BCG	652 (100)	619 (94.9)	6.6 [5.4 - 9.1]
	OPV0	652 (100)	616 (94.5)	6.3 [5.3 - 9.1]
6 weeks	OPV 1	634 (97.2)	570 (89.9)	9.0 [6.3 - 18.3]
	Rotavirus 1	634 (97.2)	494 (77.9)	8.4 [5.7 - 21.4]
	DTP/IPV/HiB 1	634 (97.2)	599 (94.5)	7.0 [4.7 - 11.2]
	Hepatitis B1	634 (97.2)	579 (91.3)	7.6 [5.9 - 13.8]
	PCV 1	634 (97.2)	546 (86.1)	8.0 [5.3 - 12.9]
10 weeks	DTP/IPV/HiB 2	594 (91.1)	537 (90.4)	7.6 [5.0 - 12.4]
	Hepatitis B2	595 (91.3)	533 (89.6)	8. 9 [5.29 - 14.3]
14 weeks	DTP/IPV/HiB 3	556 (85.3)	471 (84.7)	7.9 [5.3 - 17.1]
	Hepatitis B3	556 (85.3)	471(84.7)	7.9 [5.1 - 13.3]
	PCV 2	556 (85.3)	421 (75.7)	7.7 [5.3 - 19.9]
	Rotavirus 2	556 (85.3)	388 (69.8)	7.4 [5.1 - 19.3]
9 months	Measles 1	370 (56.7)	314 (84.9)	8.6 [5.5 - 25.3]
	PCV 3	370 (56.7)	242 (65.4)	7.3 [5.0 - 23.4]
18 months	DTP/IPV/HiB 4	232 (35.6)	167 (72.0)	10.9 [8.0 - 28.7]
	Measles 2	232 (35.6)	167 (72.0)	12.9 [6.7 - 38.6]

Immunisation coverage and timing of immunisations

The findings on vaccine coverage and timeliness of immunisation within the study population is reported for each of the age time-points indicated in the EPI-SA (Table 2).

Birth dose vaccination

Vaccination with BCG vaccine within 24 days from birth was received by 619 (94.9%) of the 652 children. Of the 619 participants who received BCG 40 (6.5%) delayed uptake of the vaccine. The OPV birth dose was received by 616 (94.5%) of the study

participants. Of the 616 participants who received OPV, 43 (7.0%) had delayed uptake of the vaccine. (Figure 2A and B).

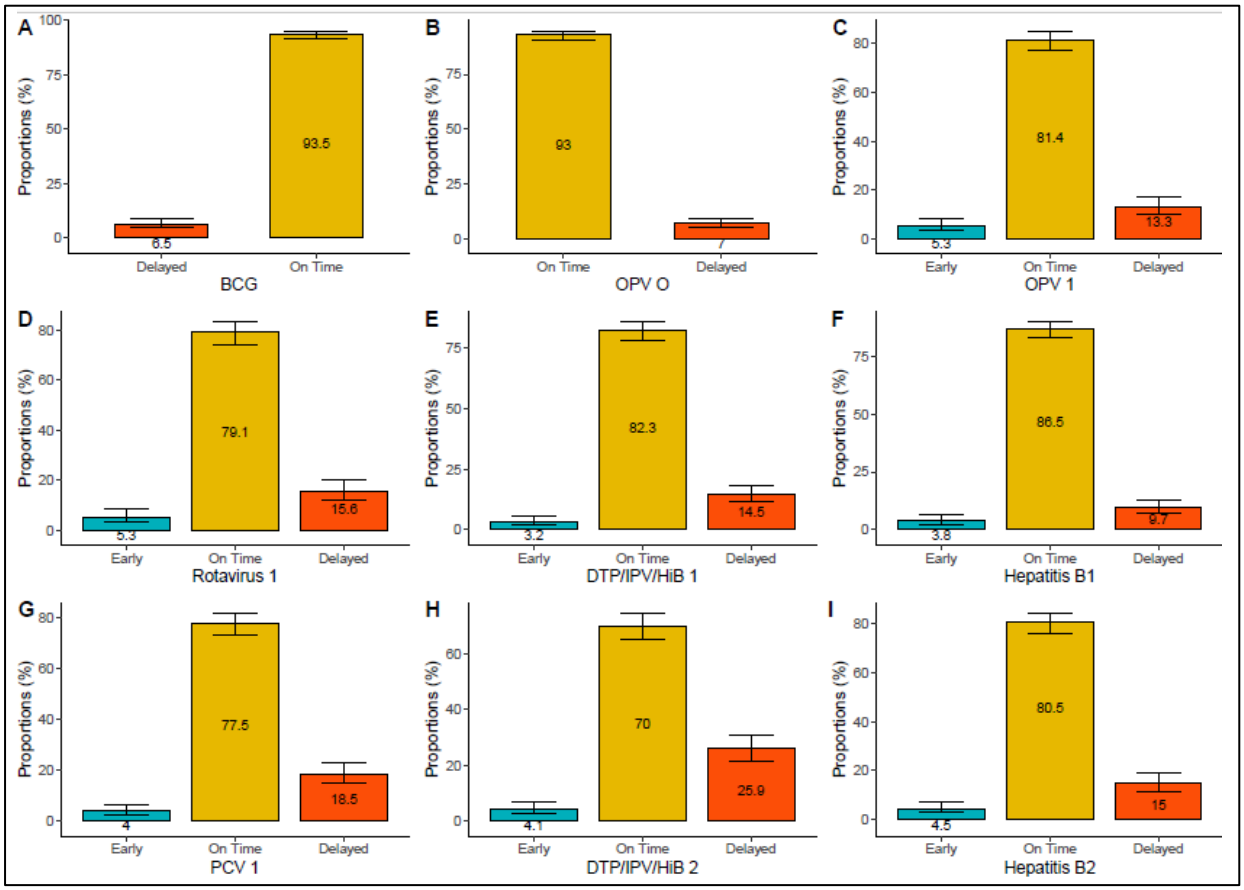

Figure 2: **Timeliness of uptake of birth, 6- and 10-week dose vaccines** BCG (n = 619); OPV (n = 616); 1st doses of Rotavirus (n = 494), DTP/IPV/HiB (n = 599), Hepatitis B (n = 579), PCV (n = 546); 2nd doses of DTP/IPV/HiB (n = 537) and Hepatitis B (n = 533).

Vaccination at 6, 10 and 14 weeks

The 1st dose of DTP/IPV/HiB was received by 599/634 (94.5%) of the eligible children, while the 1st dose of hepatitis B was received by 579/634 (91.3%), while the 1st dose of PCV was received by 546/634 (86.1%) (Table 1). Amongst those who received the 1st dose of DTP/IPV/HiB, 87 (14.5%) delayed uptake of the vaccine, 493 (82.3%) were on time, while 19 (3.2%) received the vaccine earlier than scheduled. A total of 56 (9.7%) delayed uptake for the 1st dose of hepatitis B, 501 (86.5%) of participants' vaccine uptake was on time, while 22 (3.8%) received their doses earlier than scheduled. Lastly, uptake of the 1st dose of PCV was delayed in 101 (18.5%) of participants, while 423 (77.5%) and 22 (4%) of vaccine uptake was on time and early respectively. Amongst all doses given at 6-weeks, the 1st dose of PCV had the highest

proportion of participants who delayed uptake of vaccines. The proportion of delayed participants for the 1st dose of OPV increased by 6.3% from the OPV doses given at birth. Early uptake of vaccines doses was observed in all vaccines at this 6-week age-timepoints. The highest early uptake of was among the 1st OPV and the Rotavirus vaccine doses 26 (5.3%) (Figure 2C-G).

The 2nd doses of DTP/IPV/HiB and hepatitis B had an immunisation coverage of 537/594 (90.4%) and 533/595 (89.6%) respectively (Table 1). Amongst those who received the 2nd dose of DTP/IPV/HiB and hepatitis B, 139 (25.9%) and 80 (15%) of participants delayed uptake, respectively. While 362 (70%) and 429 (80.5%) of participants had timely uptake of the vaccine doses. In addition to the decline in immunisation coverage from the 6-week age timepoint, there was also an 11.4% and 5.3% increase in delay in uptake for the 2nd DTP/IPV/HiB and hepatitis B vaccine doses respectively, compared to their 1st doses administered at the 6 weeks age timepoint. Early uptake of vaccine doses was observed to be 22 (4.1%) for the 2nd dose of DTP/IPV/HiB and 24 (4.5%) for the 2nd dose of hepatitis B (Figure 2 H and I).

The 3rd dose of the DTP/IPV/HiB vaccine was received by 471/556 (84.7%) participants. Of those, 163 (34.6%) delayed vaccine uptake, while 286 (60.7%) had timely uptake of the 3rd dose of DTP/IPV/HiB vaccine. The 3rd dose of hepatitis was received by 471/556 (84.7%), and of those, 105 (22.3%) delayed vaccine uptake, while 345 (73.2%) of participants had timely uptake of the 3rd dose of hepatitis B. Immunisation coverage for the 2nd dose of PCV was 421/556 (75.7%). Amongst those who received the 2nd dose of PCV, 117 (27.8%) delayed vaccine uptake, while 262 (62.2%) had timely uptake of the vaccine dose, as recommended. Regarding the vaccine doses administered at 14 weeks, the 3rd dose of hepatitis had the lowest proportion of participants with delayed vaccine uptake, while the 3rd dose of DTP/IPV/HiB had the highest proportion of participants who delayed vaccine uptake. When the timeliness of uptake of the vaccines administered at the 14-weeks timepoint were compared to their 10-week doses, there was an 8.7% increase for the 2nd dose of DTP/IPV/HiB, 7.3% increase for the 3rd hepatitis B dose, 9.3% increase for the 2nd PCV dose and 7.9% increase for the 2nd Rotavirus dose in delaying vaccine uptake.

The 2nd dose of PCV had the highest 42 (10%) early vaccine uptake in the 14-week age timepoint (Figure 3A-D).

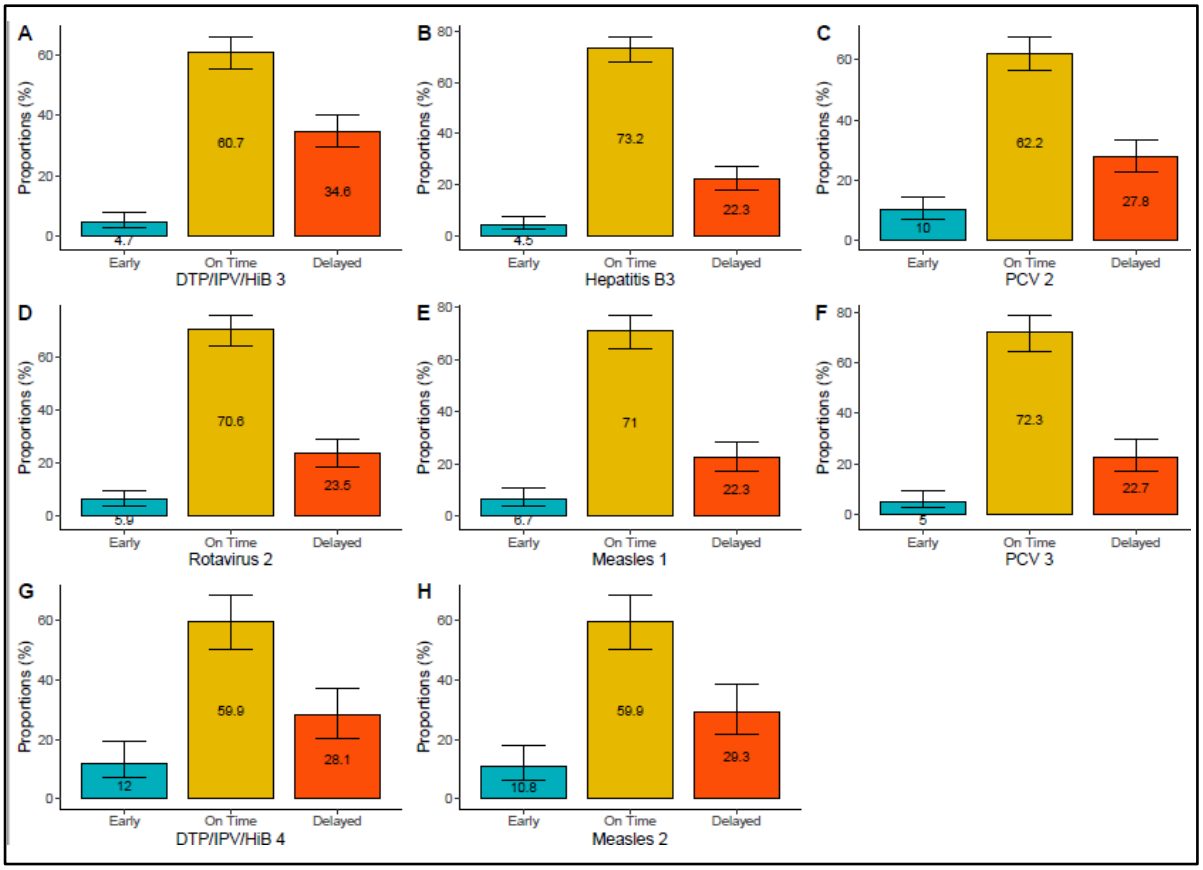

Figure 3: Timeliness of uptake for the 14 weeks, 9- and 18-month vaccine doses. 3rd doses of DTP/IPV/HiB (n = 471), and hepatitis B (n = 471), 2nd doses of PCV (n = 421), and Rotavirus (n = 388); 1st dose of Measles (n = 314), 3rd dose of PCV (n = 242); 4th dose of DTP/IPV/HiB (n = 167), 2nd dose of Measles (n = 167).

<u>Vaccination at 9 and 18 months</u>

The 1st dose of measles was received by 314/370 (84.9%). Amongst those who received the 1st dose of measles 70 (22.3%) delayed vaccine uptake, while 223 (71%) had timely uptake of the vaccine. The 3rd dose of PCV was received by 242/370 (65.4%) and of those, 55 (22.7%) of participants delayed uptake, while 175 (72.3%) had timely 3rd dose PCV vaccine uptake. While coverage of 3rd dose of PCV decreased by 10.3% between the 2nd and 3rd doses, delayed uptake reduced by 5.1% from the

14 weeks timepoint. The 1st dose of measles had 21 (6.7%) and the 3rd dose of PCV had 12 (5%) of participants who had early uptake of vaccines (Figure 3E and F).

The 2nd dose of measles and the 4th dose of DTP/IPV/HiB were both received by 167/232 (72.0%) of participants at the 18-month timepoint. Delayed uptake among the measles and the DTP/IPV/HiB doses was observed in 49 (29.3%) and 47 (28.1%) of participants, respectively. While both 2nd dose of measles and the 4th dose of the DTP/IPV/HiB had 100 (59.9%) of participants who received timely uptake of vaccines. A reduction of 12.9% for the measles dose from the 9-month age timepoint and a 12.7% reduction for the DTP/IPV/Hib dose from the 14-week age timepoint in immunisation coverage was observed for both vaccines recommended for administration at 18 months of age, but the delay in uptake of the 4th dose of DTP/IPV/HiB reduced by 6.5% compared to the 3rd dose of DTP/IPV/HiB, while the 2nd dose of measles delay in uptake increased by 7% from 1st dose. Of all the recommended age timepoints, the 18-month age timepoint had the highest early uptake of vaccines. Early vaccine dose uptake was observed in 18 (12%) for measles and 20 (10%) for DTP/IPV/HiB of this population (Figure 3G and H).

Duration of delay in age-specific immunisations

The degree of delayed age-specific routine immunisation was described using medians and inter-IQR ranges.

<u>Vaccinations at birth</u>

The median delay in uptake of BCG was 6.6 [IQR 5.4 – 9.1] weeks, while the OPV birth dose had a median delay in uptake of 6.3 [IQR 5.3 – 9.1] weeks. The median delay in uptake of the OPV birth vaccine dose was not significantly different to BCG ($p = 0.97$).

<u>Vaccinations at 6, 10 and 14 weeks</u>

It was observed that the median duration of delay in uptake of DTP/IPV/HiB doses increased with increasing age. The median duration of delay in uptake of the 1st, 2nd,

and 3rd doses of the DTP/IPV/HiB vaccine administered at 6, 10 and 14 weeks was 7.0 [IQRs 4.7 – 11.2], 7.6 [IQRs 5.0 – 12.4] and 7.9 [IQRs 5.3 – 17.1] weeks, respectively (Table 2). However, the median duration of delay between the 1st , 2nd and 3rd doses of DTP/IPV/HiB was not statistically significantly different (Figure 4). When the median duration of delay for BCG was compared with the 6 and 14 weeks doses, there was an observed significant difference for the 1st dose of OPV (p = 0.02) and the 3rd dose of DTP/IPV/HiB (p = 0.032) (Figure 4). Differences in the median duration of delays between the multiple vaccine doses was only observed among the OPV birth and the 1st OPV doses (p = 0.01) (Figure 4).

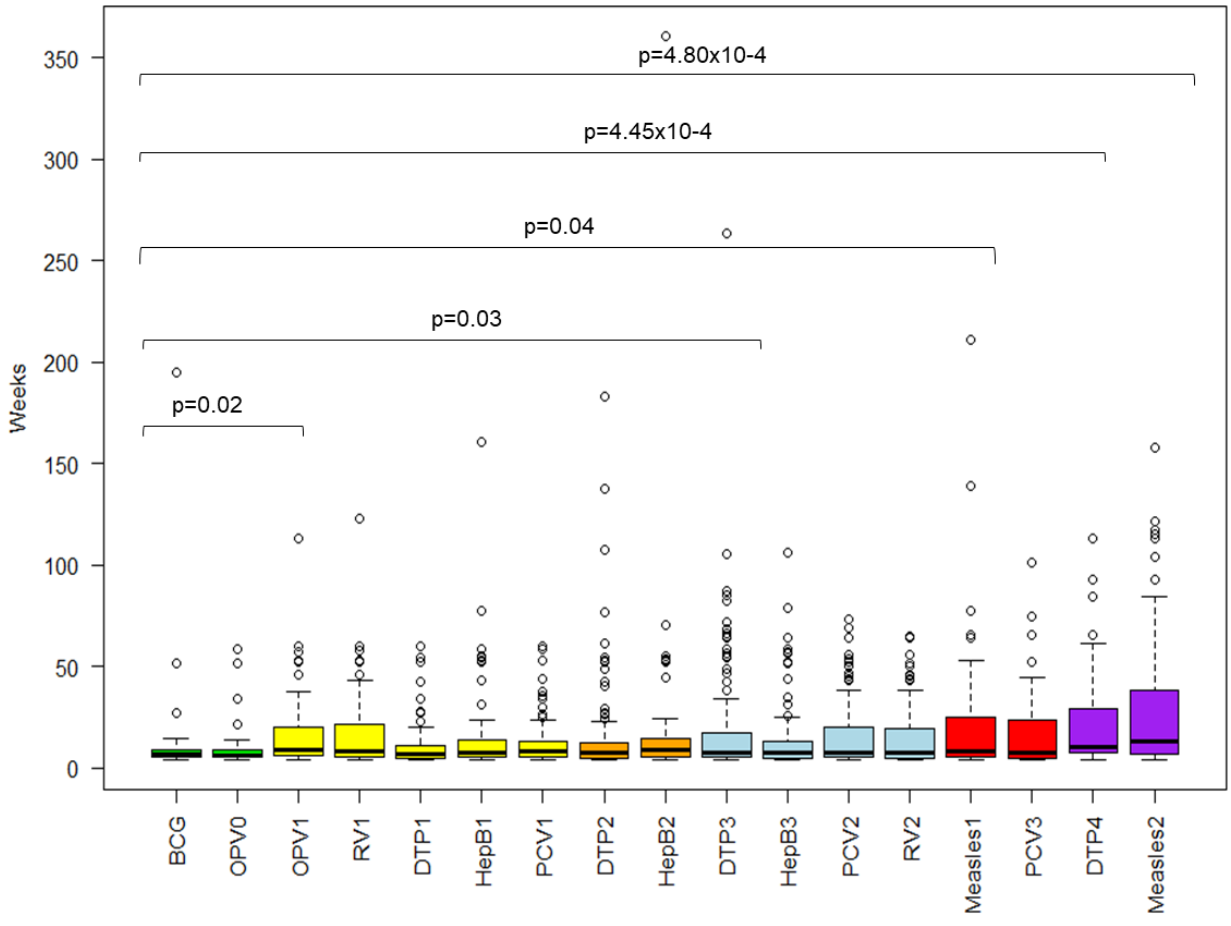

Figure 4: Change in median duration of delay in uptake of routine vaccines overtime.

Green – birth doses, yellow – 6 weeks doses, orange – 10 weeks dose, blue – 14 weeks doses, red – 9 months doses, purple – 18 months doses.

The median duration of delay in uptake of the hepatitis B vaccine increased from 7.6 [IQR 5.9 – 13.8] weeks for the 1st dose to 8.9 [IQR 5.29 – 14.3] weeks for the 2nd dose

IQRs. The median duration of delay of the hepatitis B vaccine decreased to 7.9 [IQR 5.1 – 13.3] weeks for the 3rd dose. The median difference compared to BCG and between each hepatitis B vaccine doses was not significant (Figure 4).
The median duration of delay amongst the 1st and 2nd doses of the PCV vaccines given at 6 and 10 weeks declined with increasing age. The median duration of delay in the 1st dose of PCV was 8.0 [IQR 5.3 – 12.9] weeks, while the median duration of delay for the 2nd dose of PCV was 7.7 [IQR 5.3 – 19.9] weeks (Table 2). However, the median duration of delay between 1st and 2nd doses of the PCV vaccines dose was not statistically significantly different or when the two doses were compared to BCG (Figure 4).

Vaccinations at 9 and 18 months

In general, the measles doses median delay in uptake increased with increasing age. The median duration of delay for the 9 months dose was 8.6 [IQR 5.5 – 25.3] compared to 12.9 [IQRs 6.7 – 38.8] weeks at 18 months; p=0.07. However, there was a statistically significant difference between the 1st and 2nd doses of the measles vaccines, and BCG ($p = 0.04$) and ($p = 4.80 \times 10^{-4}$), respectively (Figure 4).

The median duration of delay for the 3rd dose of PCV at 9 months further declined from the 14 weeks age timepoint from 7.7 [IQR 5.3 – 19.9] to 7.3 [IQR 5.0 – 23.4] weeks (Table 2) (Figure 4). There were no observed differences in the median duration of delay between the 2nd and 3rd doses of the PCV or when the two PCV doses were compared to BCG.

The 4th dose of the DTP/IPV/HiB vaccine had a median duration of delay that increased to 10.9 [IQR 8.0 – 28.7] weeks from the 3rd dose of the DTP/IPV/HiB vaccine of 7.9 [IQR 5.3 – 17.1] weeks. This increase in the median duration of delayed uptake was statistically significantly different between the doses ($p = 4.45 \times 10^{-4}$) and when compared to BCG ($p = 0.02$) (Figure 4).

Risk factors associated with delayed immunisations

To determine which demographic and socio-economic factors are associated with delayed immunisations, logistic regressions analyses were limited to sex, creche attendance, caregiver age, education, and SES. Where data on these variables were limited or not available, these were excluded from the analysis (Table 2). Caregivers' age was used as either a binary variable (adult/adolescent) or as a continuous variable, where data was limited.

Vaccinations at birth

None of the factors assessed were found to be statistically significantly associated with the delayed uptake of the BCG and OPV doses (Table 3).

Vaccinations at 6, 10 and 14 weeks

For the 1st Rotavirus vaccine, those raised by adults as compared to adolescent had lower odds of delaying vaccine uptake. Where the univariable analysis showed that those raised by adults had 0.29 times the odds of delaying the first dose of rotavirus vaccine (CI 0.12 – 0.72). While the multivariable analysis showed that those raised by adults had 0.33 times the odds of delaying the first dose of rotavirus vaccine (CI 0.13 – 0.94) compared to those raised by adolescents, on average (Table 3

Table 3:Logistic Regression estimates

Dose	Variable		Delayed n (%)	Univariable OR (95 % CI)	Multivariable OR (95% CI)
BCG	Sex	Male	40 (6.5)	0.52 (0.27 - 1.00)	
	Creche*	Yes		0.60 (0.24 - 1.30)	0.74 (0.26 - 1.76)
	Caregiver age*			0.98 (0.94 - 1.03)	1.00 (0.95 - 1.05)
	Caregiver age category	Adult		0.86 (0.24 - 5.49)	
	Education*	Higher		0.76 (0.04 - 3.79)	1.01 (0.05 - 6.08)
	Highest grade			1. 07 (0.86 - 1.38)	
	SES*	Low		0.99 (0.32 - 3.38)	1.06 (0.32 - 3.84)
		Lower-middle		0.57 (0.08 -2.75)	0.64(0.08 - 3.27)
		Upper-middle		1.06 (0.41 - 3.30)	0.99 (0.36 - 3.26)
OPV 0	Sex	Male	43 (6.98)	0.60 (0.32 - 1.12)	
	Creche*	Yes		0.88 (0.40 - 1.77)	1.11 (0.45 - 2.47)
	Caregiver age*			0.98 (0.94 - 1.02)	
	Caregiver age category	Adult		0.59 (0.20 - 2.55)	
	Education*	Higher		1.50 (0.23 - 5.46)	1.80 (0.25 - 7.89)
	Highest grade			1.15 (0.92 - 1.49)	
	SES*	Low		0.67 (0.23 - 1.99)	0.79 (0.26 - 2.51)
		Lower-middle		0.20 (0.01 - 1.18)	0.23 (0.01 - 1.41)
		Upper-middle		0.79 (0.33 - 2.07)	0.78 (0.31 - 2.21)
OPV 1	Sex	Male	76 (13.3)	1.42 (0.86 - 2.36)	
	Creche*	Yes		0.59 (0.31 - 1.07)	0.75 (0.38 - 1.40)
	Caregiver age			1.01 (0.98 - 1.04)	
	Caregiver age category	Adult		0.83 (0.30 - 2.91)	1.09 (0.35 - 4.80)
	Education*	Higher		1.08 (0.25 - 3.32)	1.24 (0.25 - 4.44)
	Highest grade			0.95 (0.82 - 1.12)	

	SES*	Low		0.75 (0.31 - 1.81)	0.84 (0.34 - 2.13)
		Lower-middle		0.85 (0.29 - 2.36)	0.98 (0.32 - 2.90)
		Upper-middle		0.86 (0.42 - 1.87)	0.95 (0.44 - 2.18)
Rotavirus 1	Sex	Male	77 (15.6)	0.99 (0.61 - 1.63)	
	Creche*	Yes		0.78 (0.43 - 1.42)	1.10 (0.57 - 2.03)
	Caregiver age			0.99 (0.95 - 1.02)	
	Caregiver age category	Adult		0.29 (0.12 - 0.72)	0.33 (0.13 - 0.94)
	Education*	Higher		0.35 (0.02 - 1.80)	0.36 (0.02 - 2.04)
	Highest grade			1.06 (0.89 - 1.29)	
	SES*	Low		0.45 (0.18 - 1.12)	0.41 (0.16 - 1.06)
		Lower-middle		0.54 (0.13 - 1.73)	0.47 (0.11 - 1.54)
		Upper-middle		0.82 (0.41 - 1.75)	0.74 (36 - 1.61)
DTP/IPV/HIB 1	Sex	Male	87 (14.5)	1.23 (0.77 - 1.96)	
	Creche*	Yes		1.40 (0.85 - 2.27)	1.52 (0.87 - 2.61)
	Caregiver age			1.02 (0.99 -1.04)	
	Caregiver age category			0.81 (0.32 - 2.47)	0.85 (0.31- 3.03)
	Education*	Higher		0.62 (0.10 - 2.20)	0.34 (0.02 - 1.82)
	Highest grade			1.03 (0.88 - 1.21)	
	SES*	Low		0.75 (0.33 - 1.76)	0.69 (0.27 - 1.57)
		Lower-middle		0.83 (0.29 - 2.25)	0.68 (0.23 - 1.92)
		Upper-middle		0.10 (0.51 - 2.08)	0.89 (0.44 - 1.89)
Hepatitis B1	Sex	Male	56 (9.67)	0.93 (0.54 - 1.63)	
	Race	Coloured		0.82 (0.45 - 1.46)	
	Creche*	Yes		0.49 (0.22 - 0.98)	0.59 (0.23 - 1.31)
	Caregiver age			1.03 (0.99 - 1.06)	
	Caregiver age category	Adult		0.79 (0.26 - 3.44)	0.98 (0.27 - 6.32)
	Education*	Higher		1.72 (0.39 - 5.36)	1.82 (0.36 - 6.98)
	Highest grade			0.93 (0.78 - 1.12)	
	SES*	Low		0.51 (0.19 - 1.34)	0.62 (0.22 - 1.74)
		Lower-middle		0.58 (0.15 - 1.89)	0.55 (0.11 - 2.09)

		Upper-middle		0.57 (0.26 - 1.32)	0.64 (0.28 - 1.60)
PCV 1	Sex	Male	101 (18.5)	1.13 (0.73 - 1.76)	
	Creche*	Yes		1.07 (0.63 - 1.76)	1.23 (0.69 - 2.15)
	Caregiver age			1.00 (0.98 - 1.04)	
	Caregiver age category	Adult		0.83 (0.34 - 2.31)	0.93 (0.35 - 2.90)
	Education*	Higher		0.24 (0.01 - 1.18)	0.28 (0.02 - 1.55)
	Highest grade			1.00 (0.86 - 1.17)	
	SES*	Low		1.11 (0.51 - 2.50)	0.98 (0.44 - 2.26)
		Lower-middle		1.16 (0.41 - 3.12)	0.84 (0.28 - 2.39)
		Upper-middle		1.21 - 0.62 - 2.53)	1.10 (0.55- 2.34)
DTP/IPV/HIB 2	Sex	Male	139 (25.9)	1.19 (0.81 - 1.77)	
	Creche*	Yes		0.86 (0.55 - 1.32)	0.95 (0.58 - 1.54)
	Caregiver age			0.99 (0.97 - 1.02)	
	Caregiver age category	Adult		0.79 (0.32 - 2.10)	0.82 (0.30 - 2.45)
	Education*	Higher		0.71 (0.20 - 2.01)	0.69 (0.15 - 2.42)
	Highest grade			0.89 (0.78 - 1.02)	
	SES*	Low		1.26 (0.63 - 2.57)	1.12 (0.54 - 2.37)
		Lower-middle		0.62 (0.22 - 1.60)	0.63 (0.21 - 1.68)
		Upper-middle		1.47 (0.80 - 2.79)	1.48 (0.77 - 2.81)
Hepatitis B2	Sex	Male	80 (15)	1.26 (0.78 - 2.05)	
	Creche*	Yes		0.52 (0.28 - 0.93)	0.68 (0.33 - 1.32)
	Caregiver age			0.99 (0.97 - 1.03)	
	Caregiver age category			0.51 (0.20 - 1.45)	0.60 (0.20 - 2.19)
	Education*	Higher		1.08 (0.25 - 3.35)	1.40 (0.29 - 5.25)
	Highest grade			0.87 (0.75 - 1.00)	
	SES*	Low		0.89 (0.40 - 2.04)	0.94 (0.40 - 2.28)
		Lower-middle		0.33 (0.07 - 1.11)	0.40 (0.08 - 1.43)
		Upper-middle		0.72 (0.35 - 1.56)	0.73 (0.34 - 1.67)
DTP/IPV/HIB 3	Sex	Male	163 (34.6)	1.37 (0.93 - 2.03)	

	Creche*	Yes		0.81 (0.53 - 1.23)	0.82 (0.50 - 1.35)
	Caregiver age			1.00 (0.98 - 1.03)	
	Caregiver age category			0.70 (0.27 - 1.87)	0.50 (0.15 - 1.55)
	Education*	Higher		1.12 (0.39 - 3.22)	1.13 (0.27 - 4.31)
	Highest grade			0.89 (0.78 - 1.02)	
	SES*	Low		0.97 (0.47 - 2.02)	0.93 (0.44 - 2.03)
		Lower-middle		0.61 (0.24 - 1.51)	0.52 (0.18 - 1.38)
		Upper-middle		1.24 (0.66 - 2.41)	1.34 (0.69 - 2.66)
Hepatitis B3	Sex	Male	105 (22.3)	1.34 (0.86 - 2.10)	
	Creche*	Yes		0.39 (0.22 - 0.66)	0.48 (0.22 - 0.86)
	Caregiver age			1.01 (0.99 - 1.05)	
	Caregiver age category			0.42 (0.16 - 1.18)	0.32 (0.10 - 1.06)
	Education	Higher		0.59 (0.09 - 2.24)	
	Highest grade*			0.85 (0.74 - 0.98)	0.84 (0.71 - 1.00)
	SES*	Low		1.00 (0.46 - 2.23)	0.66 (0.26 - 1.65)
		Lower-middle		0.44 (0.13 - 1.29)	0.30 (0.06 - 1.07)
		Upper-middle		0.86 (0.43 - 1.81)	0.71 (0.33 - 1.60)
PCV 2	Sex	Male	117 (27.8)	1.01 (0.66 - 1.58)	
	Creche*	Yes		0.56 (0.32 - 0.94)	0.58 (0.30 - 1.10)
	Caregiver age			1.02 (0.99 - 1.05)	
	Caregiver age category			0.55 (0.20 - 1.59)	
	Education	Higher		0.66 (0.15 - 2.22)	
	Highest grade*			0.78 (0.66 - 0.92)	0.81 (0.66 - 1.00)
	SES*	Low		2.47 (1.06 - 6.15)	1.75 (0.66 - 4.90)
		Lower-middle		1.02 (0.31 - 3.23)	1.20 (0.35 - 4.02)
		Upper-middle		2.36 (1.10 - 5.52)	2.25 (0.99 - 5.64)
Rotavirus 2	Sex	Male	91 (23.5)	0.84 (0.45 - 1.59)	
	Creche*	Yes		0.55 (0.23 - 1.17)	0.79 (0.32 - 1.80)
	Caregiver age			0.96 (0.92 - 1.00)	
	Caregiver age category *	Adult		0.30 (0.10 - 0.99)	0.45 (0.12 - 2.17)

	Education*	Higher		0.62 (0.03 - 3.31)	0.74 (0.04 - 4.58)
	Highest grade			1.08 (0.87 - 1.39)	
	SES*	Low		0.44 (0.13 - 1.41)	0.44 (0.13 - 1.44)
		Lower-middle		0.40 (0.06 - 1.83)	0.40 (0.05 - 1.87)
		Upper-middle		0.75 (0.30 - 2.04)	0.76 (0.30 -2.11)
Measles 1	Sex	Male	70 (22.3)	0.96 (0.56 - 1.65)	
	Creche*	Yes		0.78 (0.44 - 1.36)	0.99 (0.49- 1.98)
	Caregiver age			1.01 (0.87 - 1.06)	
	Caregiver age category *	Adult		0.96 (0.22 - 6.67)	0.63 (0.10 - 4.97)
	Education	Higher		0.28 (0.02 - 1.47)	
	Highest grade*			0.86 (0.72 - 1.04)	0.91 (0.71 - 1.16)
	SES*	Low		3.04 (0.98 - 11.54)	2.60 (0.64 - 13.36)
		Lower-middle		0.99 (0.18 - 4.88)	1.24 (0.20- 7.55)
		Upper-middle		3.90 (1.41 - 13.84)	4.39 (1.37 - 19.71)
PCV 3	Sex	Male	55 (22.7)	0.94 (0.51 - 1.73)	
	Creche*	Yes		0.95 (0.49 - 1.81)	1.01 (0.42 - 2.34)
	Caregiver age			1.01 (0.97 - 1.05)	
	Caregiver age category *			2.30 (0.40 - 43.59)	1.51 (0.21 - 30.70)
	Education	Higher		1.06 (0.15 - 4.77)	
	Highest grade*			0.89 (0.72 - 1.11)	1.10 (0.81 - 1.53)
	SES*	Low		3.00 (0.92 - 11.81)	5.09 (1.15 - 28.17)
		Lower-middle		1.45 (0.26 - 7.47)	1.23 (0.15 - 8.55)
		Upper-middle		2.11 (0.72 - 7.76)	2.82 (0.83 - 13.12)
DTP/IPV/HiB 4	Sex	Male	47 (28.1)	0.72 (0.36 - 1.44)	
	Creche*	Yes		0.48 (0.23 - 0.98)	0.53 (0.19 - 1.37)
	Caregiver age*			1.02 (0.97 - 1.07)	0.10 (0.97 - 1.09)
	Education*	Higher		0.59 (0.09 - 2.56)	1.17 (0.14 - 8.15)
	Highest grade			1.08 (0.85 - 1.40)	
	SES*	Low		0.64 (0.17 - 2.30)	0.35 (0.19 - 2.93)
		Lower-middle		1.20 (0.30 - 4.79)	0.76 (0.42 - 9.35)

		Upper-middle		0.42 (0.13 - 1.33)	1.96 (0.14 - 1.55)
Measles 2	Sex	Male	49 (29.3)	0.82 (0.41 - 1.63)	
	Creche*	Yes		0.49 (0.24 - 0.99)	0.37 (0.14 - 0.92)
	Caregiver age*			1.02 (0.98 - 1.08)	1.05 (0.99 - 1.12)
	Education*	Higher		0.67 (0.06 - 3.02)	1.77 (0.18 - 17.78)
	Highest grade			1.08 (0.85 - 1.39)	
	SES*	Low		1.03 (0.26 - 4.29)	1.30 (0.30 - 5.88)
		Lower-middle		1.65 (0.37 - 7.70)	2.64 (0.52 - 14.42)
		Upper-middle		1.32 (0.41 - 4.75)	1.53 (0.45 - 5.86)

*Variables adjusted for in multivariable analysis

Creche attendance compared to not attending creche was on average significantly associated with 0.52 times the odds of receiving delayed uptake of the 2nd dose of hepatitis B (CI 0.28 – 0.93). However, this protective effect was only observed in the univariable analysis model Table 3.

Regression analysis for the factors associated with delayed uptake of the 3rd dose of the hepatitis B vaccine show that attending creche compared to those who did not attend was on average statistically significantly associated with 0.39 times the odds of delaying the 3rd dose of hepatitis B vaccine in the univariable model (CI 0.22 – 0.66) While in the multivariable model, creche attendance compared to those who did not attend creche was significantly associated with 0.48 times the odds of receiving delayed uptake of the 3rd dose of the hepatitis B vaccine (CI 0.22 – 0.86). Additionally, a univariable model suggested that using grade 12 as the highest grade achievable, a decrease in caregiver grade achieved was significantly associated with 0.85 times the odds of delaying uptake of the 3rd dose of hepatitis B vaccine (CI 0.74 – 0.98).

Analysis assessing factors associated with delayed uptake of the 2nd dose of the PCV vaccine suggested that when grade 12 is used as the highest grade achievable, a unit change in the grade achieved was associated with 0.78 times the odds of delaying uptake of the 2nd dose of PCV vaccine (CI 0.66 – 0.92).Those who attended creche compared to those who did not had 0.56 times the odd of delaying uptake of the 2nd dose of PCV vaccine (CI 0.32 – 0.94). Generally, SES was a strong predictor for delayed uptake of vaccinations. Low SES compared to high SES was associated with 2.47 times the odds of delaying the 2nd dose of PCV vaccine (CI 1.06 – 6.16), while the upper-middle SES compared to higher SES had 2.36 times the odds of delaying uptake for the 2nd dose of the PCV vaccine (CI 1.10 – 5.52). These significant SES associations were observed in the univariable analysis.

A univariable regression analysis for factors associated with delayed uptake of the 2nd dose of the rotavirus vaccine suggested that having an adult caregiver, compared to an adolescent caregiver, was associated with 0.30 times the odds of delaying vaccine uptake (CI 0.10 – 0.99). This association was not observed in the multivariable analysis Table 3.

Vaccinations at 9 and 18 months

On average, those of the upper-middle SES compared to those of the high SES was statistically significantly associated with 3.90 times the odds of delaying the 1st dose of the measles vaccine (CI 1.41 – 13.84) in the univariable model. The multivariable model suggested a harmful association where those of upper-middle SES compared to those of high SES had 4.39 times the odds of delaying the 1st dose of the measles vaccine (CI 1.37 – 19.71).

In a multivariable model, those of low SES compared to those of high SES was statistically significantly associated with 5.09 times the odds of delaying uptake of the 3rd dose of the PCV vaccine (CI 1.15 – 28.17) Table 3.

Those who attended creche compared to those who did not, were significantly associated with 0.48 the odds of delaying the 4th dose of the DTP/IPV/HiB vaccine (CI 0.23 – 0.98). This protective effect was not observed in the multivariable model.

In the univariable analysis, attending creche compared to not attending creche was statistically significantly associated with 0.49 times the odds of delaying uptake of the 2nd dose of the measles vaccine (CI 0.24 – 0.99). While in the multivariable analysis, creche attendance compared to no attendance was associated with 0.37 times the odds of delaying the 2nd dose of measles vaccine (CI 0.14 – 0.92) Table 3.

Discussion

This study indicates that proportions of children with delay in timely uptake of immunisations increases with age. Similarly, the median duration of delay increased with age of vaccine doses. These trends are coupled with a decline in immunisation coverage and an increased chance of delayed subsequent doses when previous doses have been delayed. The highest coverage was seen amongst the birth doses, while the lowest was amongst the 9- and 18-months vaccine doses. Delay in receiving

doses for age was independently associated with creche attendance, having an adolescent caregiver, low and upper-middle socioeconomic quartiles.

Declining immunisation coverage with age is not unique to this study. Prior studies have reported low immunisation coverage with vaccines given at 9- and 18- months and high immunisation coverage for the birth doses [29,30]. Globally in 2015, there was a shortage of BCG vaccines, the Western Cape province had less than 50% of vials available to administer to new-borns [31]. It is highly likely that this shortage was associated with delayed uptake of the BCG vaccines in this population. To support this notion, we found a median of 6.6 [5.4 – 9.1] weeks delay in the uptake the BCG vaccine, this could be suggestive of catch-up vaccination campaigns conducted for those who were missed. Additionally, the minimum recommended time of 24 hours for the receipt of the birth dose is a contributing factor to timely uptake of vaccines in that caregiver-child pairs visit health care facilities often post-partum and as a result, missed opportunities for birth doses are a rare occurrence [32–34]. In contrast, the low immunisation coverage for the 9- and 18-month vaccines could be a result of caregivers' inability to adhere to the schedule due to busy work schedules and the caregivers lack of knowledge about VPDs at the 9- and 18-months immunisation age-timepoints [35,36]. The observed trend between the DTP/IPV/HiB doses administered at 6,10 and 14 weeks, where the delay in uptake of vaccines increased from 14.5% for the 1st dose of the DTP/IPV/HiB vaccine to 25.9% for the 2nd dose and 34.6% for the 3rd dose was not unique to our study. A Gambian study reported similar findings stating that delaying on previous doses increases the chances of delaying for the subsequent doses [37]. Additionally it is important to note that the 3rd dose of the DTP/IPV/Hib vaccine is unique in that it serves as a national immunisation marker for coverage, and it also assesses the ability of a health system to revaccinate children on multiple occasions [14]. According to our sub-optimal coverage for the 3rd dose of the DTP/IPV/Hib vaccine of less than 95%, the effectiveness of the EPI-SA in the year 2016 and its catch-up strategies remain questionable.

The observed trends of increasing delay [Highest: DTP-3 34.6% (CI 30.3-39.1) and lowest BCG: 6.5% (CI 4.7-8.8)] in the uptake of immunisation and increased time at risk of VPD was not surprising. Several studies have found similar findings where significant increases in delayed uptake of vaccine doses with age were seen, especially amongst vaccines given after the first year of life [38,39,27,40]. Due to the lack of appropriate variables or proxies in our dataset we could not assess for reasons for post-partum health care facility presentations, however drawing from similar settings, it is most likely that catch-up vaccinations (depicted as delay in uptake from the recommended time of receipt) are a result of the opportunistic presentation of caregiver-child pairs to health care facilities for other childhood sicknesses, leading to the administration of the appropriate catch-up vaccines by health care workers [38,39,40].

Timing in the 9- and 18-month immunisation age-timepoints of the immunisation is not only a concern when it comes to delayed uptake of vaccine doses, but also in the early uptake of vaccine doses. In this study, vaccine doses given at 9- and 18 months had the highest proportion of early uptake of vaccines. Due to the known high proportions of delay, early administration of measles has been observed in health care facilities as means to alleviate the delay in uptake of vaccines in some populations [7]. Prior research contradicts the early administration of measles since it has been found to confer no protection. [7,15]. It is worth noting that the thinking of lack of protection from doses given before 9 months, was around the notion of suboptimal immunogenicity and the lack of compensation from the subsequent doses in measles vaccine given at 9 months or older [19]. However, a recent systematic review and meta-analysis shows that administering the first dose of measles before 9 months can elicit a good immune response in high-risk settings; and that a subsequent dose further increases vaccine effectiveness, rather than attenuate the immune response (as was believed previously) [19]. These findings are particularly concerning from the health systems perspective. It seems health care providers were more comfortable in giving early doses to children beyond the first year of life, which at the time of data collection would be considered as malpractice. Efforts to prevent these unrecommended practices by health care workers can include adequate training about the importance of adhering

to the recommended schedule. The early administration of 18-months age-timepoint vaccines also have the potential to give an underestimation of the delayed uptake of vaccines in populations, which can subsequently affect the planning of catch-up programs.

When we explored the risk factors associated with the delay in uptake of timely vaccines, we found creche attendance to be a common protective factor in this population, from vaccines given as young as 10 weeks up to 18 months. It is not surprising to see a protective effect from creche attendance, as the Department of Basic Education in South Africa stipulates that in order to apply for admission at a public or independent school, parents or caregivers will have to provide supporting documents including an up-to-date immunisation record. Similarly, the Western Cape Education Department (WCED) has its own set of regulations which state the need of an RTHCs before registering a child in any public schools (not independent schools, as these have established their own admission rules) [24,41]. This practice leaves parents with no choice but to vaccinate their children. Having an adult caregiver was protective against delay in uptake of vaccines. Previous literature sites that having an adult caregiver of more than 35 years of age is associated with lower odds of delaying uptake of primary immunisations [42]. Low SES IQR is a frequently cited strong risk factor for delaying uptake of vaccines, as low SES is largely coupled with low education levels, and thus lack of, or limited knowledge pertaining to vaccines [16,20,43,44]. Moreover, it was surprising to see in this study that upper-middle SES IQR was harmful towards delaying uptake of vaccine doses. We could not assess the reasons for this however, it could be speculated that parents and caregivers in the upper-middle SES tend to delay or miss clinic visits due to busy work schedules. It is also possible that the older children get, the more available their caregivers become, allowing for busier work schedules [39,45]. Future studies should assess reasons for delayed or missed vaccine uptake among populations within the upper-middle SES.

Taken together, these results suggest sub-optimal immunisation coverage and lack of immunisation timeliness in this population. The considerable increased in the delay in uptake of vaccines and the increased time at risk of VPDs is concerning as it can largely contribute to the pool of infants and children susceptible to VPDs. These findings emphasize the need of an intervention (s) targeting immunisation timeliness at infancy and early childhood.

Since creche attendance conferred protection against the delay in uptake of vaccines, mitigation strategies implemented upstream by the department of basic education, as well as health and immunisation service providers should strengthen collaborations to ensure that timely vaccine uptake among creche attendees is regularly monitored. Where delays are identified, catch-up strategies can be implemented at educational facilities or referrals to immunization clinics. It is important that this strategy is coupled with caregiver and healthcare worker vaccine education on the importance of timely immunisation uptake. Education about timely vaccine uptake will aid in the provision of informed council from healthcare providers to – not only adult caregivers - but adolescent caregivers as well, with the aim to reduce delayed uptake of vaccine amongst those raised by adolescent caregiver. The health system and the EPI-SA should couple these interventions with effective mobile health strategies (i.e., mobile reminder systems). These reminder systems will particularly serve the purpose to remind those caregivers who delay uptake of vaccines as a result of a busy schedule. A recent South African multi-centre study reported the use of mobile reminders to effectively increase uptake of recommend maternal and childhood immunisations [46]. It is worth noting that in LMICs, mobile reminders have been reported to be effective only when caregivers receive two or more reminders [47]. It should be noted that alternative and complementary reminder systems may be required in settings with limited network coverage or access to mobile services.

Conclusion

We have shown that immunisation coverage and timeliness are two separate entities, which are both critical in understanding the effectiveness of routine childhood immunisation programmes in preventing the high burden of VPDs. Our findings of declining immunisation coverage, increasing delay and increased time-at-risk of VPDs with increasing age calls for immediate attention as the results have the potential to undermine the EPI-SA. Catch-up immunisation campaigns seem to be effective in minimising missed immunisation opportunities in the WCP. However, more effort is required from the health systems and immunisation service providers in firstly ensuring timely uptake to ensure optimal protection from VPDs and secondly, to ensure catch-up immunisation services are readily available and that this information is known by caregivers. Creche attendance was an important protective risk factor for the delayed uptake of vaccines in this population. This protective effect emphasises the effectiveness of the National and WC Department of Education admission policies which only allows fully immunised children into the school system. This registration policy appears to be well adhered to by caregivers of the WCP. As prior studies have shown, low SES quartiles was a strong predictor of delayed uptake of vaccines. Strategies targeting household of low SES IQRs could focus on raising awareness and continuously educating the health care workers and the general population about vaccines and the importance of timely uptake of immunisations. As effective as catch-up immunisation and the WCED immunisation registration policies are in the WCP in ensuring timely and effective catch-up immunisation campaigns, these strategies need to be coupled with reminder/mobile systems to ensure caregivers return on time for their children's vaccination. This strategy will serve as reminders to caregivers with busy work schedules. This strategy is likely to be effective in the South African context given the high cell phone coverage, as well as in other LMICs with similar contexts. Effective surveillance and monitoring of immunisation programmes at all levels is required in order to achieve effective immunisation service delivery and uptake. In the COVID-19 context in South Africa, it is particularly important to monitor the use of immunisation services at health care facilities, in order to understand the impact that the COVID-19 pandemic has had on childhood routine immunisation services.

In this study, validation of the recorded dates in the primary database was required, due to data extracting inconsistencies. We used RTHCs to obtain the date at which immunisations were received, as means of verifying date of vaccine receipt on our database. This approach can mislead the data capturing process and compromise data quality as the health care providers handwriting may not be legible. This limitation emphasise the need for electronic immunisation records [48]. This study has several strengths which are worth highlighting. Firstly, the only other South African study which evaluated vaccine timeliness in the WCP was in 2011 and conducted in the Paarl region [29]. Our study provides an update on the coverage and timeliness of routine childhood vaccines in the WCP. In addition to this, the immunisation coverage rate for "newer" vaccines gives insight on population acceptance of these vaccines which were not included at the time of the 2011 study. Secondly, quantifying delay has the potential to aid in better understanding outbreaks of VPDs reported in the Western Cape, thus informing about which age-groups should be of interest to immunisation program managers and policy makers.

The findings of this study should be considered in the context of some caveats. The study made use of a health facility-based population who may have had characteristics that are different from the general population. In addition to this, the geographical focus of the study was restricted to the WCP which may not be representative of all provinces in South Africa.

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PART C: Appendices

Appendix 1: Case Report Form

CASE REPORT FORM

STUDY TITLE	
Pertussis in children hospitalised with Lower Respiratory Tract infection (LRTI)	
Study reference number:	**371/2011**

CLINICAL TRIAL SITE/UNIT:	Red Cross War Memorial Children's Hospital Department of Paediatrics University of Cape Town Klipfontein Road Rondebosch, 7700
PRINCIPAL INVESTIGATOR:	Rudzani Muloiwa

Patient's Name Hospital sticker	

Subject Study Number:	☐☐☐☐☐☐☐

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: _____

Date of signature: ☐☐☐☐☐☐☐☐

d d m m y y y y

Parent contact details& Inclusion criteria

Care giver's First and Middle Names: _____

Care giver's Last Name: _____

Home Address *(If different from child's address)*

_____

_____

_____

Home Telephone Number: _____

Work Telephone Number: _____

Cellular Telephone Number: _____

Alternate contact details

1. Name _____ Relationship _____

   Home Telephone Number: _____

   Work Telephone Number: _____

   Cellular Telephone Number: _____

Inclusion Criteria		**Yes**	**No***
1	Is the subject a child aged 13 years or younger?	☐	☐
2	Has the subject's parent/legal guardian willingly given written informed consent?	☐	☐
3	Has the subject been admitted for LRTI or apnoea?	☐	☐

If any inclusion criteria are ticked 'No' then the patient is not eligible for the study.

Exclusion Criteria		**Yes***	**No**
1	Is child too ill to be enrolled?	☐	☐
2	Has the child been admitted for more than 72 hours?	☐	☐

If any exclusion criteria are ticked 'Yes' then the patient is not eligible for the study.

1. Parent Interview Form

Pertussis study number: __ __ __ __: __ __ __

A. GENERAL: *Complete all questions*

1.	Are you the primary caregiver for this child?	☐ Yes	☐ No
2.	What is your relationship to him or her?	☐ Mother ☐ Grandparent ☐ Caregiver	☐ Father ☐ Other relative ☐ Other:
3.	During the first 4 months of life, how was your child fed?	☐ Breast milk ☐ Formula (never breastfed)	☐ Breast milk and formula ☐ Unknown
4.	If older than 4 months: how is your child being fed at present? (*In addition to solids*)	☐ Breast milk ☐ Formula ☐ Unknown	☐ Breast milk and formula ☐ Other: _____ ☐ Not applicable
5.	What is your house made of?	☐ Bricks ☐ Tin/iron sheeting ☐ Unknown	☐ Mud/traditional ☐ Other: _____
6.	How many people sleep in the same room as the child *(not counting the child)?*	_____ people	☐ Unknown
7.	Do you use any of the following for heating and/or cooking in the household? (*check all that apply*)	☐ Electricity ☐ Coal ☐ Wood ☐ Unknown	☐ Gas ☐ Paraffin ☐ Other: _____
8.	What is the main source of water in the household?	☐ In-door tap water ☐ River water ☐ Other:	☐ Borehole ☐ Outdoor/communal tap ☐ Unknown
9.	What type of toilet do you have at the house?	☐ Flush toilet ☐ Bucket system ☐ Other:	☐ Pit latrine ☐ None/ Outdoors ☐ Unknown
10.	Does the person who usually cares for the child smoke inside the house?	☐ Yes ☐ No	☐ Unknown
11.	Does anyone else smoke inside the house?	☐ Yes ☐ No	☐ Unknown
12.	Does your child attend a nursery or crèche?*(at least 2 other children for at least 4 hours per day, 3 days per week)*	☐ Yes ☐ No	☐ Unknown
13.	What is the highest level of education the mother has completed?	☐ No School ☐ Higher education ☐ Unknown	☐ Schooling: highest grade completed ___ ___

B. MEDICAL HISTORY

14.	Did your child have any of the following symptoms during the current illness?				
14.1	Fever	☐ Yes	☐ No	☐ Unknown	*(skip to 14.2 if No or Unknown)*
14.1.1	*If yes:* Duration	_____ days		☐ Unknown	
14.2	Cough	☐ Yes	☐ No	☐ Unknown	*(skip to 14.3 if No or Unknown)*
14.2.1	*If yes:* Duration	_____ days		☐ Unknown	
14.2.2	Night time cough	☐ Yes	☐ No	☐ Unknown	
14.2.3	Paroxysms of cough	☐ Yes	☐ No	☐ Unknown	
14.2.4	Whooping cough	☐ Yes	☐ No	☐ Unknown	
14.2.5	Vomiting after cough	☐ Yes	☐ No	☐ Unknown	
14.2.6	Facial cyanosis	☐ Yes	☐ No	☐ Unknown	
14.2.7	Barking cough	☐ Yes	☐ No	☐ Unknown	
14.2.8	Normal state between cough	☐ Yes	☐ No	☐ Unknown	
14.3	Apnoea *(stopping breathing)*	☐ Yes	☐ No	☐ Unknown	
14.4	Loss of weight	☐ Yes	☐ No	☐ Unknown	
14.5	Fits (seizures)	☐ Yes	☐ No	☐ Unknown	
14.6	Presence of any of these symptoms	☐ Runny nose ☐ Sneezing	☐ Wheeze ☐ None	☐ Fast breathing ☐ Unknown	
15.	Did you seek health care prior to this hospitalization?	☐ Yes	☐ No	☐ Unknown	*(skip to 16 if No or Unknown)*

Staff initials: __ __ __ Date completed: __ __ / __ __ / 20 __ __

1. Parent Interview Form – (continue)

15.1	*If Yes*, did you go to:	☐ Clinic ☐ Traditional healer ☐ General practitioner ☐ Other:
16.	Did the child receive an antibiotic before coming to the hospital?	☐ Yes, oral antibiotic ☐ Unknown *(skip to 17 if No or Unknown)* ☐ Yes, injection ☐ No ☐ Unknown
16.1	*If Yes*, name of antibiotic *If Yes*, number of days on antibiotics?	_____ days ☐ Unknown
17.	Does your child take cotrimoxazole (bactrim)?	☐ Yes ☐ No ☐ Unknown *(skip to 18 if No or Unknown)*
17.1	*If Yes*, for how long?	____ months or ____ weeks ☐ Unknown
18.	Has any one at home been coughing for more than two weeks? If yes, how many people? Relationship with coughing person/s	☐ Yes ☐ No ☐ Unknown _____
19.	Has your child been in contact with an adult known to have TB in the past 6 months?	☐ Yes ☐ No ☐ Unknown *(skip to 19 if No or Unknown)*
19.1	*If Yes*, is the person with TB currently on treatment?	☐ Yes ☐ No ☐ Unknown
20	Is your child currently receiving INH prophylaxis	☐ Yes ☐ No ☐ Unknown *(skip to 19 if No or Unknown)*
20.1	*If Yes*, about how long has your child been taking it?	____ months or ____ weeks ☐ Unknown
21	Has the child ever been admitted to hospital? *(Before this admission)*	☐ Yes ☐ No ☐ Unknown *(skip to 20 if No or Unknown)*
21.1	*If Yes*,	
21.2	How long ago was the last admission?	____ months ____ weeks ____ days ☐ Unknown
21.3	Number of previous hospitalizations (*not including current illness*):	☐ 1-2 ☐ 3-5 ☐ >5 ☐ Unknown
21.4	Were any of these previous admissions for apnoea?	☐ Yes ☐ No ☐ Unknown
21.5	Were any of these previous admissions for a chest infection?	☐ Yes ☐ No ☐ Unknown
22	Has your child ever been diagnosed with one of the following chronic medical conditions? *(before this admission)*	☐ TB Disease: *If yes*: ☐ On treatment ☐ Completed treatment ☐ Defaulted ☐ Asthma ☐ Heart problem ☐ Pertussis/Whooping cough ☐ Other lung problems Specify _____ ☐ Cerebral palsy ☐ Malnutrition ☐ Kidney problem Specify _____ ☐ Other Specify _____ ☐ None known
23	Did the child's mother have an HIV test during pregnancy?	☐ Yes ☐ No ☐ Unknown *(skip to 22 if No or Unknown)*
23.1	*If Yes*, what was the latest result?	☐ Positive ☐ Negative ☐ Unknown
24	Has the child ever been tested for HIV?	☐ Yes ☐ No ☐ Unknown *(skip to end if No / Unknown)*
24.1	*If Yes*, What was the result?	☐ Positive ☐ Negative ☐ Unknown *(skip to end if Neg / Unknown)*
25	Is the child currently receiving Antiretroviral Therapy (ART)?	☐ Yes ☐ No ☐ Unknown *(skip to end if No / Unknown)*
25.1	For how long has the child taken ART?	_____ months ☐ Unknown

2. RTHC / Vaccination History

Pertussis study number: __ __ __ __: __ __ __

1.	Does the child have a road to health card available?	☐ Yes *(Skip to 2)* ☐ No
1.1	*If No,* Has the child ever received any vaccines other than the vaccines *he or she* received at birth?	☐ Yes ☐ No ☐ Unknown

Copy the following information from the card, if no RTHC available, ask person completing interview

2.	Date of Birth (dd/mm/yy)	__ __ / __ __ / 20__ __	☐ Unknown
2.1	If DOB unknown, enter age in months:	_____	
3.	Is the child failing to thrive/crossing centiles	☐ Yes ☐ No	☐ Unsure
4.	Birth weight	___ . ___ ___ kg	☐ Unknown
5.	Gestational age	___ ___ weeks	☐ Unknown
5.1	If gestational age unknown	☐ Term ☐ Premature (<37 weeks)	☐ Unknown

If the RTHC is available, please complete ☐ **No RTHC available**

6.	Vaccine		Date given (dd/mm/yyyy)	
6.1	BCG		__ __ / __ __ / 2 0 __ __	☐ Not given
6.2	OPV	0	__ __ / __ __ / 2 0 __ __	☐ Not given
		1	__ __ / __ __ / 2 0 __ __	☐ Not given
		2	__ __ / __ __ / 2 0 __ __	☐ Not given
		3	__ __ / __ __ / 2 0 __ __	☐ Not given
		4	/ / 2 0	☐ Not given
6.3	PENTAXIM LOCATION GIVEN	-	*(i.e Health facility where the child*	*received vaccine)*
6.3	_____	1	__ __ / __ __ / 2 0 __ __	☐ Not given
	_____	2	__ __ / __ __ / 2 0 __ __	☐ Not given
	_____	3	__ __ / __ __ / 2 0 __ __	☐ Not given
	_____	4	__ __ / __ __ / 2 0 __ __	☐ Not given
	OR _____			
	DTP/HIB _____	1	__ __ / __ __ / 2 0 __ __	☐ Not given
	_____	2	__ __ / __ __ / 2 0 __ __	☐ Not given
	_____	3	__ __ / __ __ / 2 0 __ __	☐ Not given
	DTP	4	/ / 2 0	☐ Not given
6.4	PCV ☐ 7 ☐ 13 ☐ Unknown	1	__ __ / __ __ / 2 0 __ __	☐ Not given
	☐ 7 ☐ 13 ☐ Unknown	2	__ __ / __ __ / 2 0 __ __	☐ Not given
	☐ 7 ☐ 13 ☐ Unknown	3	/ / 2 0	☐ Not given
6.5	ROTAVIRUS	1	__ __ / __ __ / 2 0 __ __	☐ Not given
		2	__ __ / __ __ / 2 0 __ __	☐ Not given
6.6	MEASLES	1	__ __ / __ __ / 2 0 __ __	☐ Not given
		2	/ / 2 0	☐ Not given
7.	INFLUENZA	1	__ __ / __ __ / 2 0 __ __	☐ Not given
		2	__ __ / __ __ / 2 0 __ __	☐ Not given
8.	OTHER: _____		__ __ / __ __ / 2 0 __ __	
9.	Did the child have any of the following within 6 weeks before or after any of the vaccines in 6.3?		☐ Steroid use ☐ Immunoglobulin therapy ☐ Other: _____	☐ Measles ☐ None ☐ Unknown
	If yes, which vaccines? Enter 1- 4		_____	
10.	Has the child received Vitamin A in the previous six months?		☐ Yes ☐ No	☐ Unknown

Staff initials: __ __ __ Date completed: __ __ / __ __ / 20 __ __

3. Medical Records

The following questions relate to the current admission. Information should be obtained from clinical records or measured (e.g. weight and temperature) if not available in records. Temperature, heart rate and respiratory rate should be the maximum recorded within 24 hours of admission

Pertussis study number: __ __ __ __: __ __ __

1.	Sex	☐ *Male* ☐ *Female*
2.	Date of admission	___ ___ / ___ ___ / 2 0 ___ ___ *(dd/mm/yyyy)*
3.	Time of admission	___ ___ : ___ ___ ☐ *Am* ☐ *Pm* ☐ *Unknown*
4.	Race	☐ *Asian/Indian* ☐ *Black* ☐ *White* ☐ *Coloured*
5.	Admission height/length	___ ___ . ___ *cm*
6.	Admission weight	___ ___ . ___ *kg*
7.	Mid upper arm circumference (MUAC)	___ ___ . ___ *cm*
8.	Head Circumference	___ ___ . ___ *cm*
9.	Temperature	___ ___ . ___ *°C*
10.	Heart rate	___ ___ ___ *beats / min* ☐ *Not recorded*
11.	Respiratory rate	___ ___ ___ *breaths / min* ☐ *Not recorded*
12.	Oxygen saturation	___ ___ ___ *%* ☐ *Room air* ___ ___ ___ *%* ☐ *On oxygen* ☐ *Not recorded*
13.	Presence of oedema	☐ *Yes* ☐ *No* ☐ *Not recorded*
14.	Did the child receive any of: Bronchodilators Antibiotics *If Yes*, name of antibiotic	 ☐ *Yes* ☐ *No* ☐ *Yes* ☐ *No* _____
15.	HIV Stage of the child	☐ *1* ☐ *2* ☐ *3* ☐ *4* ☐ *Not Applicable*

16.	Lower chest wall indrawing:	☐ *Yes* ☐ *No* ☐ *Not recorded*
17.	Crackles/crepitations	☐ *Yes* ☐ *No* ☐ *Not recorded*
18.	Wheezing	☐ *Yes* ☐ *No* ☐ *Not recorded*
19.	Clubbing	☐ *Yes* ☐ *No* ☐ *Not recorded*

***Outcome Summary** – to be obtained on all participants when discharged.*

20.	Did child receive supplemental oxygen	☐ *Yes* ☐ *No* ☐ *Not recorded*
21.	Admission to a High Care unit or ICU If admitted to above, number of days	☐ *ICU* ☐ *High Care* ☐ *None* ☐ *Unknown* *ICU days:* ____ *High Care days:* ____ ☐ *Unknown*
22.	Assisted ventilation If Yes, Duration Type of support Number of days	☐ *Yes* ☐ *No* ☐ *Not recorded* _____ *days* ☐ *Not recorded* ☐ *CPAP* ☐ *IPPV* _____ *days* _____ *days* ☐ *Not recorded*
23.	Outcome of child	☐ *Discharged* ☐ *Refused Hospital Treatment (RHT)* ☐ *Died* ☐ *Transferred to another hospital*
24.	Date of discharge/ death/ transfer/RHT	___ ___ / ___ ___ / 2 0 ___ ___ *(dd/mm/yyyy)*
25.	If discharged, on what treatment was child discharged? *(mark all that apply)*	☐ *Antibiotics, specify:*_____ ☐ *Bronchodilators* ☐ *Inhaled steroids* ☐ *Anti TB treatment* ☐ *Other, specify*
26.	*Discharge diagnosis (mark all that apply)*	☐ *Bronchopneumonia* ☐ *Bronchiolitis* ☐ *Lobar Pneumonia* ☐ *Tuberculosis* ☐ *Pertussis* ☐ *Pneumocystis pneumonia* ☐ *Chronic lung disease* ☐ *Sepsis* ☐ *Underweight/Kwashiorkor/Marasmus* ☐ *Not recorded* ☐ *Other, specify*_____

Staff initials: __ __ __ Date completed: __ __ / __ __ / 20 __ __

4. Care-Giver Information

Pertussis study number: __ __ __ __: __ __ __

1.	Sex	☐ *Male* ☐ *Female*
2.	Date of birth	___ ___ / ___ ___ / 19 ___ ___ *(dd/mm/yyyy)*
3.	What is your relationship to child	☐ Mother ☐ Father ☐ Grandparent ☐ Other relative ☐ Caregiver ☐ Other: _____
4.	Race	☐ *Asian/Indian* ☐ *Black* ☐ *White* ☐ *Coloured*
5.	Do you sleep in the same room as child?	☐ *Yes* ☐ *No*
6.	Do you smoke? If Yes, do you smoke inside the house?	☐ *Yes* ☐ *No (skip to next question if No)* ☐ *Yes* ☐ *No*
	Did you experience any of these symptoms before or during the course of the child's illness?	
7.	Fever?	☐ *Yes* ☐ *No* ☐ *Unknown*
8.	Wheezing?	☐ *Yes* ☐ *No* ☐ *Unknown*
9.	Runny or congested nose?	☐ *Yes* ☐ *No* ☐ *Unknown*
10.	Cough?	☐ *Yes* ☐ *No* ☐ *Unknown* *(skip to 11 if No or Unknown)*
	If Yes, duration?	_____ *days* _____ *weeks* ____ *months* ☐ *Unknown*
10.1	Night time cough	☐ Yes ☐ No ☐ Unknown
10.2	Paroxysms of cough	☐ Yes ☐ No ☐ Unknown
10.3	Whooping cough	☐ Yes ☐ No ☐ Unknown
10.4	Vomiting after cough	☐ Yes ☐ No ☐ Unknown
10.5	Barking cough	☐ Yes ☐ No ☐ Unknown
10.6	Normal state between cough	☐ Yes ☐ No ☐ Unknown
10.7	Did you receive any of the following: Bronchodilators Antibiotics *If Yes*, Name of antibiotic	☐ *Yes* ☐ *No* ☐ *Yes* ☐ *No* _____
11.	Have you ever been diagnosed with one of the following chronic medical conditions?	☐ TB Disease: *If yes:* ☐ On treatment ☐ Completed treatment ☐ Defaulted ☐ Asthma ☐ Other lung problems ☐ Pertussis/Whooping cough ☐ Heart problems ☐ None ☐ Other, *Specify* _____
12.	Have you ever had an HIV test?	☐ Yes ☐ No
13.	*If Yes,* what was the result of the latest test?	☐ Positive ☐ Negative
14.	Are you currently receiving Antiretroviral Therapy (ART)?	☐ Yes ☐ No

5. Investigations & Results Form

Pertussis study number: __ __ __ __: __ __ __

Questions 1 and 2 to be completed for all participants

1.	**HIV testing** ☐ **Not done** *(skip to 2)*		
	Test	Date of test	Result
1.1	☐ ELISA – child	__ __/ __ __/ 2 0 __ __	☐ Reactive ☐ Non reactive
1.2	☐ ELISA - mother	__ __/ __ __/ 2 0 __ __	☐ Reactive ☐ Non reactive
1.3	☐ PCR - child	__ __/ __ __/ 2 0 __ __	☐ Positive ☐ Negative
1.4	☐ Most recent CD4 count - child	__ __/ __ __/ 2 0 __ __	_____ Absolute CD4 __ __.__ % of lymphocytes
1.5	☐ Most recent viral load - child:	__ __/ __ __/ 2 0 __ __	_____ copies/ml ☐ >750 000

2.	**Micro/Virology results** - *Obtained in the first 48 hours of admission* ☐ **Not done** *(skip to 3)*			
	Lab number	Date of test	Site	Organism
2.1		__ __/ __ __/ 2 0 __ __		
2.2		__ __/ __ __/ 2 0 __ __		
2.3		__ __/ __ __/ 2 0 __ __		
2.4		__ __/ __ __/ 2 0 __ __		

3.	**CRP (C-reactive protein)** *(<72 hrs of admission)* ☐ **Not done** *(skip to 4)*			
	Date __ __/ __ __/ 2 0 __ __	Time__ __: __ __ ☐ Am ☐ Pm ☐ Not recorded		Result___ ___ ___ mg/l
3.1	**Haematology**	**Result**		
3.1	Haemoglobin	_____		
3.2	Platelets	_____		
3.3	White cell count	_____ (Total)		
4.	Differential count	Lymphocytes	Absolute _____	Percentage _____
4.1		Neutrophils	Absolute _____	Percentage _____
4.2		Monocytes	Absolute _____	Percentage _____
4.3		Bands	Absolute _____	Percentage _____
4.4		Other	Absolute _____	Percentage _____
5.	**STUDY SPECIMENS TAKEN**	Date __ __/ __ __/ 2 0 __ __		
		☐ NP Swab for culture ☐ Induced sputum	☐ NP Swab for PCR (Child) ☐ NP Swab for PCR (Care-Giver)	

6.	**TB Results** ☐ **Not done** *(skip to 6)*			
	Date	Specimen	Result –AFB smear	Culture requested
6.1	__ __/ __ __/ 2 0 __ __	☐ Induced sputum ☐ Gastric Washings ☐ Not recorded	☐ Positive ☐ Negative	☐ Yes ☐ No

7.	**Other** *(skip to 8 if not done)*		
	Test	Date of test	Result
7.1	☐ Albumin	__ __/ __ __/ 2 0 __ __	___ ___ . ___ g/dL
7.2	☐ Total protein	__ __/ __ __/ 2 0 __ __	___ ___ . ___ g/dL
7.3	☐ Chemistry	__ __/ __ __/ 2 0 __ __	Na ____ K ____ Urea ____ Creatine ____

8.	**Radiology**		
8.1	Date of chest x-ray	__ __/ __ __/ 2 0 __ __	
8.2	X-ray findings	☐ Normal ☐ Pleural effusion ☐ Cavitations ☐ Sub-optimal quality	☐ Interstitial infiltrate ☐ Consolidation or air bronchograms ☐ Lobar consolidation ☐ Other

Staff initials: __ __ __ Date completed: __ __/ __ __/ 2 0 __ __

Appendix 2: Ethics Clearance Certificate

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

Room G50-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 January 2020

HREC REF:027/2020

A/Prof R Muloiwa
Division of Paediatrics & Child Health
G26, NGSH

Dear A/Prof Muloiwa

PROJECT TITLE: DESCRIPTIVE ANALYSIS OF ROUTINE CHILDHOOD IMMUNISATION TIMELINES IN THE WESTERN CAPE, SOUTH AFRICA. (SUB-STUDY 371/2011) (MPH DEGREE - NTOMBI BLOSE)

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

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

Approval is granted for one year until the 30 January 2021.

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

The HREC acknowledge that the student: Ntombi Blose will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

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

Yours sincerely

Signature Removed

pp
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

HREC 027/2020sa

Appendix 3: South African Expanded Programme on Immunisation Schedule from April 2009

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

Expanded Programme on Immunisation – EPI (SA)
Revised Childhood Immunisation Schedule from April 2009

Age of Child	Vaccines needed	How and where is it given?
At Birth	BCG Bacilles Calmette Guerin	Intradermal / Right arm
	OPV (0) Oral Polio Vaccine	Drops by mouth
6 Weeks	OPV (1) Oral Polio Vaccine	Drops by mouth
	RV (1) Rotavirus Vaccine	Liquid by mouth
	DTaP-IPV//Hib (1) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and *Haemophilus influenzae* type b Combined	Intramuscular / Left thigh
	Hep B (1) Hepatitis B Vaccine	Intramuscular / Right thigh
	PCV7 (1) Pneumococcal Conjugated Vaccine	Intramuscular / Right thigh
10 Weeks	DTaP-IPV//Hib (2) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and *Haemophilus influenzae* type b Combined	Intramuscular / Left thigh
	Hep B (2) Hepatitis B Vaccine	Intramuscular / Right thigh
14 Weeks	RV (2) Rotavirus Vaccine*	Liquid by mouth
	DTaP-IPV//Hib (3) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and *Haemophilus influenzae* type b Combined	Intramuscular / Left thigh
	Hep B (3) Hepatitis B Vaccine	Intramuscular / Right thigh
	PCV7 (2) Pneumococcal Conjugated Vaccine	Intramuscular / Right thigh
9 Months	Measles Vaccine (1)	Intramuscular / Left thigh
	PCV7 (3) Pneumococcal Conjugated Vaccine	Intramuscular / Right thigh
18 Months	DTaP-IPV//Hib (4) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and *Haemophilus influenzae* type b Combined	Intramuscular / Left arm
	Measles Vaccine (2)	Intramuscular / Right arm
6 Years (Both boys and girls)	Td Vaccine Tetanus and reduced strength of diphtheria Vaccine	Intramuscular / Left arm
12 Years (Both boys and girls)	Td Vaccine Tetanus and reduced strength of diphtheria Vaccine	Intramuscular / Left arm

DISCONTINUED

* Rotavirus Vaccine should NOT be administered after 24 weeks.

sanofi pasteur
The vaccines division of sanofi-aventis Group

Appendix 4: Vaccine journal author guidelines

VACCINE

The official journal of The Edward Jenner Society and The Japanese Society for Vaccinology.

AUTHOR INFORMATION PACK

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ISSN: 0264-410X

DESCRIPTION

Vaccine has an open access mirror journal Vaccine: X which has the same aims and scope, editorial board and peer-review process. To submit to Vaccine: X visit https://ees.elsevier.com/jvacx

Vaccine is **unique** in publishing the highest quality science across **all disciplines** relevant to the field of vaccinology - all original article submissions across basic and clinical research, vaccine manufacturing, history, public policy, behavioral science and ethics, social sciences, safety, and many other related areas are welcomed. The submission categories as given in the Guide for Authors indicate where we receive the most papers. **Papers outside these major areas are also welcome and authors are encouraged to contact us with specific questions**. We also invite authors **to submit relevant basic science and clinical reviews, methodological articles, opinion and commentary pieces, visual pieces, and letters**. Authors are required to consult the Guide for Authors as the submission guidelines are dynamic and therefore subject to change.

The Editors retain the right to desk reject submissions without peer review when it is clear that the Guide for Authors **and the** submission categories ***have not been consulted***.

AUDIENCE

Research workers, product developers, clinicians and practitioners with interests in virology, bacteriology, parasitology, mycology, immunology, genetics, biotechnology and biochemistry in the medical and veterinary fields.

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ABSTRACTING AND INDEXING

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Biotherapeutic and vaccine technology, protein technologies, virus-like particle

Anton P. J. Middelberg, The University of Adelaide Faculty of Engineering Computer and Mathematical Sciences School of Chemical Engineering and Advanced Materials, Adelaide, South Australia, Australia

Bioprocessing, virus-like particles, biomanufacturing, vaccines, bionanotechnology

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Study Design, Biostatistical Methods, Vaccine Safety, Vaccine Effectiveness,

Surveillance **Arthur Reingold**, University of California Berkeley, Berkeley, California, United

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adjuvants; liposomes; antibodies to lipids; antibodies to drugs of abuse; vaccine carriers

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polio eradication, rubella and CRS elimination, measles elimination, new vaccine introduction, surveillance of VPDs

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Bacterial Pathogenesis, Mucosal Immunity, Innate Immune Responses

Robert L. Atmar, Baylor College of Medicine Department of Molecular Virology and Microbiology, Houston, United States

influenza, norovirus, respiratory viruses, enteric viruses

Ian G. Barr, Victorian Infectious Diseases Reference Laboratory, North Melbourne, Australia

Influenza, vaccines, RSV, respiratory disease, serology

Noel Barrett, Baxter Innovations GmbH Orth an der Donau, Orth an der Donau, Austria

Preclinical and Clinical Vaccine Development, Influenza Vaccines, Lyme Disease Vaccines, Flavivirus Vaccines, Alphavirus Vaccines

Kenneth Beagley, Queensland University of Technology Institute of Health and Biomedical Innovation, Brisbane, Australia

Vaccines for sexually transmitted infection, Mucosal vaccines, Transcutaneous vaccination, Development of novel adjuvants

Martin Beer, Friedrich-Loeffler-Institute Federal Research Institute for Animal Health, Greifswald, Germany

Veterinary vaccines, especially vaccines against avian and swine influenza, pestvirus vaccines, orbivirus vaccines, and ", recombinant viral vaccines", 1.Virology, especially the field of Pestiviruses (BVDV, CSFV, BDV), Influenza viruses (animal influenza A viruses) , Orbiviruses (e.g., Bluetongue virus), Schmallenberg virus 2.Vaccines for viral diseases (especially “recombinant vaccines”) 3.Diagnostics for viral diseases (especially “molecular diagnostics”)

Igor Belyakov, Consultant Company for Immunology and Vaccine Development, Gaithersburg, Maryland, United States

mucosal vaccines, viral immunology and vaccines, HIV/SIV vaccines, adjuvant, CD8+CTL and MHC class I

Paolo Bonanni, University of Florence Department of Health Sciences, Firenze, Italy

Vaccination strategies, surveillance, economics, safety

Xavier Bosch, Catalan Institute of Oncology Cancer Epidemiology Research Programme, Barcelona, Spain

HPV

Prosper Boyaka, OHIO STATE UNIVERSITY, Columbus, United States

Innate regulation of mucosal immune responses, Adjuvants and mucosal vaccines, Mucosal immunity and allergy, Microbiota

David Briles, The University of Alabama at Birmingham, Birmingham, United States

Streptococcus pneumoniae, virulence, host immunity, vaccines, virulence factors, mechanisms of virulence, vaccine antigens

Alexander Bukreyev, University of Texas Medical Branch, Galveston National Laboratory, Gaveston, United States

Virus, Vaccine, Ebola, Respiratory Syncytial Virus, Pathogenesis, Antibody.

Antonella Caputo, University of Ferrara Department of Chemical and Pharmaceutical Sciences, Ferrara, Italy

Vaccine development, preclinical model, immune responses, nano-micro particles, viral infections

Antonio Cassone, University of Perugia, Perugia, Italy

Parasitic and Immune-mediated Diseases

Yung-Fu Chang, Cornell University, Ithaca, United States

Microbial pathogenesis, vaccine and adjuvant, glycoengineering vaccine, animal models, proteomics.

Allan Cripps, Griffith University - Gold Coast Campus, Southport, Australia

Mucosal immunology, lung, middle ear, gastrointestinal tract, conjugate vaccines, oral vaccines, microbiome, probiotics, immune modulation, inflammation.

Roy Curtiss III, University of Florida, Gainesville, United States

Biotechnology, genetics, microbiology, immunology,

vaccinology **Ron Dagan**, Soroka Medical Center, Be'er Sheva,

Israel

Pediatric infectious diseases, Vaccines, Respiratory infections, Otitis media, Streptococcus pneumoniae disease and prevention

Pierre van Damme, University of Antwerp, Wilrijk-Antwerp, Belgium

Epidemiology, prevention, infectious diseases

Amanda Dempsey, University of Colorado Denver - Anschutz Medical Campus, Aurora, United States

Pediatrics, Immunization Delivery

Betty Dodet, Dodet Bioscience, Caluire et Cuire, France

Biology – Vaccinology – Experimental Cancerology – Public health

Philippe Duclos, World Health Organization Department of Immunization Vaccines and Biologicals, Genève 27, Switzerland

Policies and strategies, vaccine efficacy and effectiveness, vaccine safety, post-market surveillance, decision making epidemiology and modeling

Kathryn M. Edwards, Vanderbilt University School of Medicine, Nashville, United States

Pertussis disease and vaccines; Influenza vaccines; Adjuvants; Vaccine safety; Pediatric vaccines

Barbara Ensoli, National Institute of Health HIV and AIDS Research Center, Roma, Italy

Virology, Immunology

Ian Hector Frazer, The University of Queensland Diamantina Institute, Brisbane, Australia

Immunotherapy Viruses Cancer Vaccines

Immunoregulation **Tong-Ming Fu**, Sanofi Pasteur Biologics Co,

Cambridge, United States Virus, neutralization, monoclonal

antibodies, adjuvants, T-cells

Jose de la Fuente, University of Castilla La Mancha Research Institute of Hunting Resources, Ciudad Real, Spain

Molecular biology, vaccinology, immunology, biotechnology, tick

Kohtaro Fujihashi, The University of Alabama at Birmingham, Birmingham, United States

Mucosal vaccine development, Mucosal infection and immunity, Oral tolerance, T cells and dendritic

cells

James Galen, University of Maryland Baltimore, Baltimore, United States

Genetic engineering of bacterial protein expression systems (both chromosomal and plasmid-based), Salmonella vaccines (typhoidal and non-typhoidal), bacterial live vector-based vaccines

Adolfo Garcia-Sastre, Icahn School of Medicine at Mount Sinai Department of Microbiology, New York, United States

RNA viruses, influenza, vaccines, virus immunity, host-virus interactions

John W. Glasser, Centers for Disease Control and Prevention, Atlanta, United States Infectious diseases, mathematical modeling, public policy

Dan Granoff, UCSF Benioff Children's Hospital Oakland, Oakland, United States

Meningococcal Vaccines. Factor H binding Protein

Marie Griffin, VANDERBILT UNIVERSITY MEDICAL CENTER, Nashville, United States

Pharmacoepidemiology, Vaccine Safety, Geriatrics

Carlos Guzman, Helmholtz Centre for Infection Research Department of Vaccine and Applied Microbiology, Braunschweig, Germany

adjuvants, mucosal adjuvants, mucosal delivery, humanized mice

Robert Hall, National Institute of Allergy and Infectious Diseases, Bethesda, United States

Cholera, E. coli, enteric bacteria

Scott Halperin, Dalhousie University, Halifax, Canada

Bacteriology, Vaccinology, Pertussis, Clinical Trials Immunization, Meningococcal Vaccine, Influenza Vaccine

Ali Harandi, University of Gothenburg, Gothenburg, Sweden

1. Vaccine adjuvants 2. mucosal immunity and vaccines 3. genital tract immunity 4. vaccine against genital herpes

Jorma Hinkula, Linköping University, Linköping, Sweden

Virology, Vaccines, Monoclonal antibodies, Mucosal immunity, Animal models, Antivirals

Kiyoko Iwatsuki-Horimoto, The Institute of Medical Science The University of Tokyo, Tokyo, Japan

Influenza, Negative strand RNA virus, Molecular biology

Lisa Jackson, Kaiser Permanente Washington Health Research Institute, Seattle, United States

Influenza vaccines, pneumococcal vaccines, vaccine safety

Rodrigo Jiménez-García, Rey Juan Carlos University, Madrid, Spain

Influenza vaccines, pneumococcal vaccine, epidemiological studies on vaccine coverage, vaccnes in high risk groups such as diabetics, COPD sufferers or heart disease sufferers.

Mark Jit, Public Health England, London, United Kingdom

Mathematical modelling, health economics and national decision making around vaccination programmes. Vaccine-preventable diseases I am particularly familiar with are, HPV, rotavirus, pneumococcus, influenza (seasonal and pandemic), tuberculosis and measles

Yoshihiro Kawaoka, University of Wisconsin at Madison, School of Veterinary Medicine; Influenza Research Inst., Dept. of Pathobiological Sciences, Madison, United States

Influenza and Ebola viruses

Stephen Kent, The University of Melbourne Department of Microbiology and Immunology, Melbourne, Australia

HIV vaccines, macaques, SIV, ADCC antibodies

Ki Hong Kim, Pukyong National University, Busan, Korea, Republic of

Recombinant or attenuated bacterial vaccines in fish, recombinant or attenuated viral vaccines in fish, vaccines against parasitic diseases in fish, immunostimulats and adjuvants used for fish and shellfish, RNA interference-mediated protection against viral diseases in fish

Dennis Klinman, Frederick National Laboratory for Cancer Research, Frederick, United States

DNA vaccines, Antrax vaccines, TLR-based vaccine adjuvants (particularly CpG ODN), whole-cell based cancer vaccines

Keith Klugman, Bill and Melinda Gates Foundation, Pneumonia program, Seattle, United States

pneumococcal conjugate vaccine, typhoid Vi vaccine

Eiji Konishi, Osaka University Research Institute for Microbial Diseases, Osaka, Japan

flavivirus, mosquito-borne virus, DNA vaccine

Thomas Lehner, Guy's Hospital, London, United Kingdom

vaccination against HIV or SIV, the effect of stress on immunity, mechanism of immunological memory

Margaret Liu, Karolinska Institute, Stockholm, Sweden

DNA vaccines, T cell immunity, vacciens for HIV and influenza, immunotherapy, Prime boost immunization

Pier Luigi Lopalco, European Centre for Disease Prevention and Control, Solna, Sweden

vaccine preventable disease epidemiology, vaccine preventable disease surveillance, post-marketing vaccine monitoring, epidemiological aspects of vaccination

Shan Lu, University of Massachusetts Medical School, Worcester, United States Vaccines, HIV, influenza, biodefense agents, emerging

infectious diseases. **Raina MacIntyre**, University of New South Wales, Sydney, Australia

Adult immunisation, influenza, herpes zoster, pneumococcal disease, vaccines

Helena Maltezou, National Public Health Organization, Athens, Greece

Healthcare personnel vaccinations, influenza epidemiology, pregnant women, vaccination policies

Tetsuro Matano, National Institute of Infectious Diseases AIDS Research Center, Tokyo, Japan

HIV vaccine, viral vector vaccine, T-cell responses, monkey AIDS model

Peter McIntyre, Children's Hospital at Westmead, Westmead, Australia

Immunisation Registers, Serosurveillance, Vaccine effectiveness, Pertussis, Pneumococcal infections

Dennis Metzger, Albany Medical College, Albany, United States

respiratory tract and approaches to induce protection against pulmonary pathogens, including influenza virus and Streptococcus pneumoniae, as well as to prevent deadly co-infections by those two pathogens

Mark Miller, National Institutes of Health, Bethesda, United States

vaccine policy and economics, including health outcomes; International programs and vaccines; Computational biology and mathematical modelling of vaccine programs

Anthony Newall, University of New South Wales, Sydney, Australia

Infectious diseases, economic evaluation, cost-effectiveness, epidemiology, vaccine-preventable diseases

Peter Newman, University of Toronto, Toronto, Canada

HIV

Slobodan Paessler, UNIVERSITY OF TEXAS MEDICAL BRANCH AT GALVESTON, Galveston, United States

RNA viruses, encephalitic viruses, hemorrhagic viruses, respiratory viruses

Peter Palese, Icahn School of Medicine at Mount Sinai, New York, United States

Antivirals, Apoptosis/Cell Death, Biodefense, Coronavirus, Influenza Virus, Interferon, Interferon Antagonists, Nipah Virus, Paramyxovirus, RNA, SARS Virus, Vaccine Development, Virulence Genes

Marcela Pasetti, University of Maryland Baltimore, Baltimore, United States

Vaccine Immunology, pediatric vaccines, maternal-infant immunity, correlates of protection, mucosal immunity

Stephen Pelton, Boston Medical Center, Boston, United States

pneumococcal disease, colonization and prevention (specifically in children), acute otitis media, chronic suppurative otitis media, meningococcal disease and vaccines, epidemiology, treatmemnt and prevention of HIV in children

Michael Pichichero, Rochester General Hospital Research Institute, New York, United States

Bacterial respiratory bacteria, streptococcus pneumonia, haemophilus influenza, Moraxella catarrhalis, group A streptococcus, Pertussis, pediatric vaccines, immunology of vaccine responses in neonates and children

Stanley Plotkin, Sanofi Pasteur, Doylestown, United States

Rubella, Cytomegalovirus, Pertussis, Rotavirus

Maarten Postma, University of Groningen, Groningen, Netherlands

pharmacoeconomics; health economics; reimbursement; health technology assessment; mathematical modelling

Nicola Principi, University of Milan, Milan, Italy

Pediatrics, Infectious Diseases, Vaccines, Antibiotics, Immunology

Roman Prymula, Charles University Faculty of Medicine in Hradec Kralove Department of Social Medicine, Hradec Králové, Czech Republic

pneumococcal vaccines, MMRV, TBE vaccines, meningococcus B vaccines

Rino Rappuoli, GSK Vaccines SRL, Siena, Italy

bacterial toxins, infectious diseases, reverse vaccinology

Steven Reed, Infectious Disease Research Institute, Seattle, United States

Immunological response to mycobacteria infections

Guus Rimmelzwaan, University of Veterinary Medicine, Research Center for Emerging Infections and Zoonoses, Hannover, Germany

Virus, Infection, Vaccines, Immunity, T cells

Lance Rodewald, Centers for Disease Control and Prevention, Atlanta, United States

Any study with coverage as an outcome, Provider knowledge, attitude and practise studies, Studies about parental confidence in vaccines, Global vaccination studies - related to the Expanded Program on Immunization priorites, Polio eradication and measles elimination studies

Ted Ross, Vaccine and Gene Therapy Institute of Florida, Port Saint Lucie, United States

Development of Broadly Reactive Vaccines, COBRA modeling, Influenza, HIV, Dengue.

Mark Rozenbaum, Pfizer BV, Capelle Aan Den Ijssel, Netherlands

health economics/cost effectiveness evaluations, pneumococcal and pertussis vaccines, epidemiology of pneumococccal and pertussis disease

Xavier Saelens, Ghent University, Gent, Belgium

1. Influenza A and B vaccine development (preclinical research) 2. Vaccine development against human and bovine Respiratory Syncytial virus 3. Innate immunity against influenza and RSV, e.g. applied as adjuvant strategies 4. State of the art recombinant vaccine antigen expression systems

William Schaffner, Vanderbilt University School of Medicine, Nashville, United States

Infectious Disease, Preventative Medicine, Immunization Policy

David Scheifele, BC Children's Hospital, Vancouver, Canada

vaccine trials in children and adults, especially those involving influenza, meningococcal, pneumococcal and combination childhood vaccines

Claire-Anne Siegrist, University of Geneva Center of Vaccinology and Neonatal Immunology, Genève, Switzerland

vaccine immunology, neonatal immunology, vaccine adjuvants

Mark Slifka, Oregon Health & Science University Oregon National Primate Research Center, Beaverton, United States

Neutralizing antibody responses, CD8+ T cell responses, arenaviruses, flaviviruses, clinical studies, mouse models

Kanta Subbarao, National Institute of Allergy and Infectious Diseases, Bethesda, United States

Influenza; Pandemic influenza; SARS coronavirus

Andreas Suhrbier, QIMR Berghofer Medical Research Institute, Herston, Australia

alphaviruses, inflammation, cancer

Rik de Swart, Erasmus Medical Center Department Viroscience, Rotterdam, Netherlands

Measles, morbillivirus pathogenesis, immunosuppression, respiratory syncytial virus, host response

GUIDE FOR AUTHORS

INTRODUCTION

Vaccine has an open access mirror journal, JVAC: X. ***Vaccine*** is the most comprehensive and pre-eminent journal for those interested in vaccines and vaccination, serving as an interface between academics, those in research and development, regulatory and governmental agencies, charities, and health and industry professionals.

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