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Los Angeles

Impact of an Emergency Strategy to Revitalize the Routine Immunization System of the Democratic Republic of the Congo, the “Mashako Plan” Policy

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Sylvia Marie Tangney

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ABSTRACT OF THE DISSERTATION

Impact of an Emergency Strategy to Revitalize
the Routine Immunization System of the
Democratic Republic of the Congo, the "Mashako Plan" Policy

by

Sylvia Marie Tangney
Doctor of Philosophy in Epidemiology
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Professor Anne W. Rimoin, Chair

Background: Vaccines have been a major medical achievement in modern history, significantly reducing the spread of infectious diseases worldwide. Routine immunization (RI) systems have become a global standard for providing consistent access to vaccination services and protecting communities against vaccine-preventable diseases. The Democratic Republic of Congo (DRC) is the largest country in sub-Saharan Africa with an estimated population between 86 to 106 million and a median age of 17 years. DRC has struggled with low vaccination coverage, with only 35-45% of children being fully immunized for all antigens in the DRC RI schedule. To address this challenge with childhood immunization coverage, the Congolese government, DRC national immunization program worked in conjunction with international partners to develop the Mashako Plan, an emergency strategy to revitalize the routine immunization system. The policy targets key areas such as vaccine availability, equity in vaccination services, monitoring and

evaluation, workforce development, and data quality and management. Since its initial rollout of the Mashako Plan in 2018, there have been very few formal evaluations to understand the impact of the policy on the DRC RI system. **Methods:** By utilizing monthly District Health Information Software 2 (DHIS2) administrative data and Expanded Programme on Immunizations (EPI) mobile supervision data, this study assesses the efficacy of the Mashako plan on the RI system in the DRC. Descriptive analyses of the EPI mobile supervision data identify trends in RI process indicators and an interrupted time series analysis assesses the impact of the Mashako plan on vaccine doses administered for pentavalent (penta) vaccine doses 1 and 3 and measles vaccine. Pentavalent vaccine is a conjugate vaccine that includes Diphtheria, Pertussis, Tetanus, Hepatitis B and Hib and is given at 6, 10 and 14 weeks in the DRC RI system. Furthermore, a comparative interrupted time series analysis determines the effect of the rotavirus vaccine on diarrheal disease cases in children under 5 years of age in Mashako and non-Mashako Plan provinces. **Results:** The study found that the mean number of immunization sessions held per health facility in each province remained stable over time, irrespective of the COVID-19 pandemic. The availability of vaccines and refrigerators also remained constant during the study period, while health area supervision activities decreased in late 2021, coinciding with internal healthcare worker strikes in DRC. The descriptive analyses of the EPI mobile supervision data showed that the majority of process indicators remained stable or improved over time, including the availability of vaccines and essential supplies. The interrupted time series analysis showed that the implementation of the Mashako Plan was associated with a significant increase in the percentage change of third doses of pentavalent vaccine administered per health facility per month. The baseline percentage change in doses administered at the time of Mashako Plan implementation were 4.3% for penta3, 3.4% for penta1, and 4.9% for measles vaccine. For each additional year of the policy, there was

an increase of 3.8% in the percent change of penta3 doses, 3.8% in the percent change of penta1 doses, and 2.2% in the percent change of measles vaccine doses administered above the background rate of increase. The comparative interrupted time series analysis revealed that for the non-Mashako provinces, the implementation of rotavirus vaccine introduction has a negative effect on the incidence of simple diarrhea cases (IRR=0.984), indicating a 1.6% reduction in the incidence of simple diarrhea cases each month may be attributed to the introduction of the rotavirus vaccine. However, in the Mashako group, the IRR for simple diarrhea cases shows a small negative effect (IRR=0.999), indicating a 0.1% reduction in the incidence rate of simple diarrhea each month after rotavirus vaccine introduction may be attributed to the vaccine introduction. However, both groups were very close to null and an ITS analysis with all provinces controlling for Mashako implementation month showed no impact. **Conclusion:** The results of this study describe the overall initial impact of the Mashako plan in strengthening the RI system in DRC. These analyses demonstrate the influence of cross-cultural and cross-sectoral collaborations on vaccination services. Overall, the studies demonstrate the importance of vaccination programs and interventions in improving public health outcomes in DRC and the need for monitoring and evaluating the impacts of these programs to ensure their success and sustainability. Despite regional differences, the overall positive results provide confidence in the Mashako activities and support the implementation of the next phase of Mashako 2.0. Additional studies should be conducted to assess the regional impacts of the Mashako Plan in DRC.

The dissertation of Sylvia Marie Tangney is approved.

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DEDICATION

To my family and friends, my support network that has gotten me through the stress, anxiety, and tears with laughter, late night phone calls, and unconditional love. This accomplishment is not mine alone, I will always be grateful for your presence in my life and for the countless ways in which you have helped me grow. Thank you, I would not be where I am without you.

TABLE OF CONTENTS

LIST OF TABLES ix

LIST OF FIGURES x

ACKNOWLEDGEMENTS xii

VITA xiv

Chapter 1: Introduction 1

1.1 OVERVIEW OF DRC 1

1.3 THE EXPANDED PROGRAMME ON IMMUNIZATION IN DRC 5

1.4 MASHAKO PLAN BACKGROUND AND IMPLEMENTATION 7

1.5 THESIS RATIONALE 10

1.6 DATA SOURCES 12

Chapter 2: Understanding Routine Immunization Patterns in 9 "Mashako" Provinces: Insights from EPI Mobile Supervision in the Democratic Republic of the Congo 15

2.1 ABSTRACT 15

2.2 BACKGROUND 17

2.3 METHODS 19

2.4 RESULTS 21

2.5 DISCUSSION 23

2.6 CONCLUSION 26

Chapter 3: The Impact of the Emergency Strategy "Mashako Plan" to Revitalize the Routine Immunization System in DRC: An Interrupted Time Series Analysis 38

3.1 ABSTRACT 38

3.2 BACKGROUND 40

3.3 METHODS 41

3.4 RESULTS 44

3.5 DISCUSSION 48

3.6 CONCLUSION 51

Chapter 4: Rotavirus vaccine introduction in the DRC: a comparative interrupted time series analysis 65

4.1 ABSTRACT 65

4.2 BACKGROUND 67

4.3 METHODS **70**
4.4 RESULTS **74**
4.5 DISCUSSION **76**
4.6 CONCLUSION **83**

Chapter 5: Conclusion **108**
5.1 MAIN RESULTS **108**
5.2 STRENGTHS **109**
5.3 LIMITATIONS **110**
5.4 CONCLUSION **110**

References **113**

LIST OF TABLES

Page

CHAPTER 1

Table 1: DRC Routine Immunization Schedule 6

Table 2: Aims Overview 11

CHAPTER 2

Table 1. EPI Mobile Supervision Data 9 Mashako Province Observations, Jan 2019-Dec 2021 27

Table 2. Linear Models to test for trend, mean doses over time 30

CHAPTER 3

Table 1. Estimates from ITS Analysis by Antigen. 58

CHAPTER 4

Table 1. Results of Comparative Interrupted Time Series Analyses for Simple, Dehydrated and Severe Dehydrated Diarrheal Cases in Children under 5 years, per 10,000 population 91

Table 2. Expanded ITS Analyses, Rotavirus vaccine introduction event of interest (January 2020), controlling for season and Mashako plan implementation, January 2018-March 2022 95

LIST OF FIGURES

Page

CHAPTER 1

Figure 1. Population Distribution of DRC 1

Figure 2. Map of DRC Provinces 2

Figure 3: WHO Recommended Routine Immunizations for Children 4

Figure 4: MICS 2017-18 Full Vaccination Coverage in DRC 6

Figure 5: Mashako Plan Policy Implementation Timeline 9

Figure 6: Dissertation Schematic 12

CHAPTER 2

Figure 1. WHO COVID-19 Dashboard 27

Figure 2. Number of Health Areas Supervised 28

Figure 3. Mean Immunization Sessions plotted over time with trend lines of vaccine doses. 29

Figure 4. Percentage of Facilities with Refrigerators and Functioning Refrigerators 31

CHAPTER 3

Figure 1. Map Mashako Province Rollout 52

Figure 2: DAG of Interrupted Time Series Analysis of the Impact of Plan Mashako on percent change in vaccine coverage (penta3, penta1, measles) 53

Figure 3a: Penta3 Percent Change in doses administered from baseline year (year before Mashako implementation) to each subsequent year 54

Figure 3b: Penta1 Percent Change in doses administered from baseline year (year before. Mashako implementation) to each subsequent year 54

Figure 3c: Measles Percent Change in doses administered from baseline year (year before. Mashako implementation) to each subsequent year 55

Figure 4a. Plot of percent change in the percent of Penta3 doses administered, comparing baseline (2018) to each subsequent year 56

Figure 4b. Plot of percent change in the percent of Penta1 doses administered, comparing baseline (2018) to each subsequent year 57

Figure 4c. Plot of percent change in the percent of Measles doses administered, comparing baseline (2018) to each subsequent year 57

CHAPTER 4

Figure 1. Map of initial 9 Mashako Plan Provinces 84
Figure 2. DAG 85
Figure 3. Autocorrelation Test Plots 86
Figure 4. Panelview plot 87
Figure 5a. Parallel Trend Plots 88

Figure 5b. Parallel Trend Plots 89

Figure 5c. Parallel Trend Plots 90

Figure 6. Comparative Interrupted Time Series Analysis for outcome Simple Diarrheal Disease cases per 10,000 population in children under 5 years, stratified by season (rainy season=0, dry season=1) 92

Figure 7. Comparative Interrupted Time Series Analysis of Dehydrated Diarrheal 93

Disease Cases (Mashako vs. Non-Mashako) in children under 5 years, per 10,000 population, stratified by season

Figure 8. Comparative Interrupted Time Series Analysis of Severe Dehydrated 94

Diarrhea, stratified by Season (0=Rainy Season, 1=Dry Season)

Figure 9a. Maps of Simple Diarrheal Disease Cases Over Time 96

Figure 9b. Maps of Dehydrated Diarrheal Disease Cases Over Time 96

Figure 9c. Maps of Severely Dehydrated Diarrheal Disease Cases Over Time 96

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Publications and Presentations

1. Lame P, Milabyo A**, Tangney S**, Mbaka G, Luhata C, Le Gargasson J et al. A successful national and multi-partner's approach to increase immunization coverage: The Democratic Republic of Congo "Mashako Plan" 2018-2020. Global Health Science and Practice. 2023 Mar 7.
2. Barrall AL, Hoff NA, Nkamba DM, Musene K, Ida N, Bratcher A, Dzogang C, **Tangney S**, Beia M et al. Hesitancy to receive the novel coronavirus vaccine and potential influences on vaccination among a cohort of healthcare workers in the Democratic Republic of the Congo. Vaccine. 2022 Aug 12;40(34):4998-5009. doi: 10.1016/j.vaccine.2022.06.077. Epub 2022 Jul 1. PMID: 35840471; PMCID: PMC9247270.
3. **Tangney S**, Barrall A et al. Levels of knowledge and availability of information related to COVID-19 vaccination among healthcare workers in the Democratic Republic of Congo. Poster Presentation, Elsevier 16th Vaccine Congress, Riva Del Garda Congress Centre, Lake Garda, Italy, 2022.
4. Barrall A, Nkamba D. M., Hoff N., Doshi R., Dhalke M., **Tangney S**. et al. Phone-based survey results about perceived COVID-19 knowledge and vaccination status in the Democratic Republic of the Congo. Poster Presentation (presented by S Tangney), Elsevier 16th Vaccine Congress, Riva Del Garda Congress Centre, Lake Garda, Italy, 2022.
5. **Tangney S**, Barrall A et al. Information sources and vaccine hesitancy among healthcare workers in the Democratic Republic of Congo. Poster Presentation, Elsevier 15th Vaccine Congress (held via zoom), Riva Del Garda Congress Centre, Lake Garda, Italy, 2021
6. Newman C, **Tangney S**. Applications of Most Significant Change to evaluate the successes and challenges of a large-scale global immunization systems strengthening program. Panel Presentation, American Evaluation Association Conference, Cleveland, OH, 2018.

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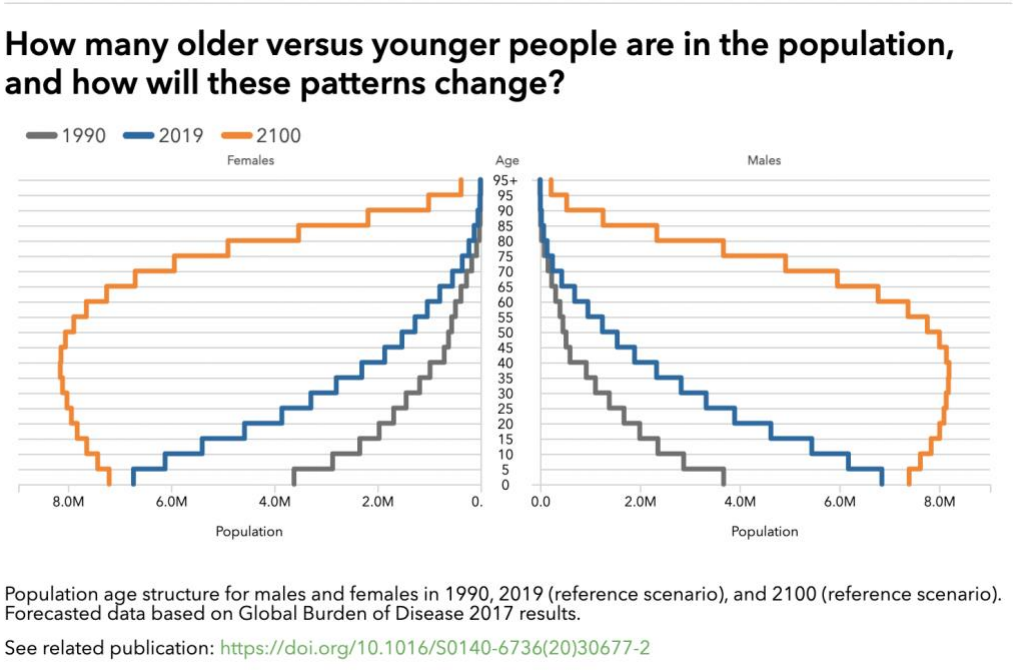
2022-2023	Dissertation Year Fellowship Award, UCLA

Chapter 1: Introduction

1.1 OVERVIEW OF DRC

The Democratic Republic of the Congo (DRC) is the largest country in sub-Saharan Africa covering the same land mass as the entirety of Western Europe and population estimates ranging from 86 to 106 million people[1,2]. The DRC shares land borders with 9 different countries and these borders are fluid[3]. In 2020 2.2 million people were newly displaced in Eastern Congo and there were the highest number of internally displaced people (IDPs) since 2016[4]. On the 2020 Human Development Index, DRC ranks 175 out of 189[1]. With an estimated birth rate of 6 births per woman, the DRC has one of the highest fertility rates in the world[2]. In part because of this high birth rate, the median age in DRC is 17 years old and the population is becoming younger as time goes on (Figure 1) [5].

Figure 1: Population Distribution of DRC[5]

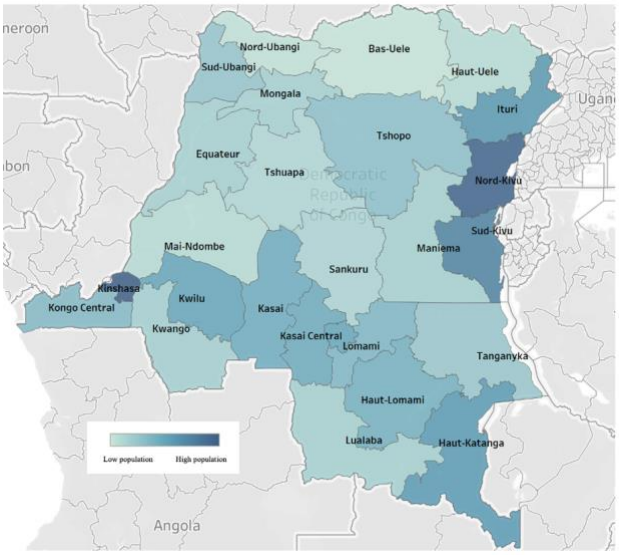


Population age structure for males and females in 1990, 2019 (reference scenario), and 2100 (reference scenario). Forecasted data based on Global Burden of Disease 2017 results.

See related publication: https://doi.org/10.1016/S0140-6736(20)30677-2

The DRC is made of 26 provinces (Figure 2), a transition from 11 provinces that occurred in practice in 2015, and these 26 provinces contain 519 health zones and 8971 health areas[6]. DRC has experienced 3 large measles outbreaks since 2011 and its 15th Ebola outbreak as of September of 2022[7–9]. The 2017-2018 Multiple Indicator Cluster Surveys (MICS) found that the average full vaccination coverage of all provinces to be around 35%[10,11]. The persistent outbreaks, fragile system and young population make a strong immunization system a critical part of a strong overall health system in DRC.

Figure 2: Map of DRC Provinces[12]



1.2 Routine Immunization

Vaccination in some capacity has existed for centuries. While some form of variolation or intentional exposure to disease as a form of prevention has existed since sometime around the year 1000, the first smallpox vaccine was developed in the 1700's and several vaccines were recommended in many countries by the 1900s, the routine immunization system as we know it today within the present health system has only existed since the mid-1900s[13]. Routine immunization forms the foundation of a country's ability to administer life-saving vaccines to its population regularly[14]. By establishing a standard immunization schedule, countries are able to systematically control and eradicate vaccine-preventable diseases (VPDs), thereby reducing the morbidity and mortality related to VPDs[14]. Routine immunization (RI) systems account for most immunizations given in most countries and are often touted as the backbone of health initiatives, they account for significant decreases in

vaccine preventable disease (VPD) morbidity and mortality and are much more cost effective than mass immunization campaigns and supplemental immunization activities (SIAs)[15]. According to the Centers for Disease Control and Prevention (CDC), 2.5 million vaccine preventable deaths are prevented through routine immunization systems around the world each year[16]. Between 2000 and 2008, World Health Organization (WHO) estimates that 12.7 million measles deaths were prevented globally by vaccination; 66% of cases were prevented by keeping the RI system functioning at the level it was in 2000, while the additional 33% were averted through the combination of increasing RI coverage and supplemental measles immunization activities[15].

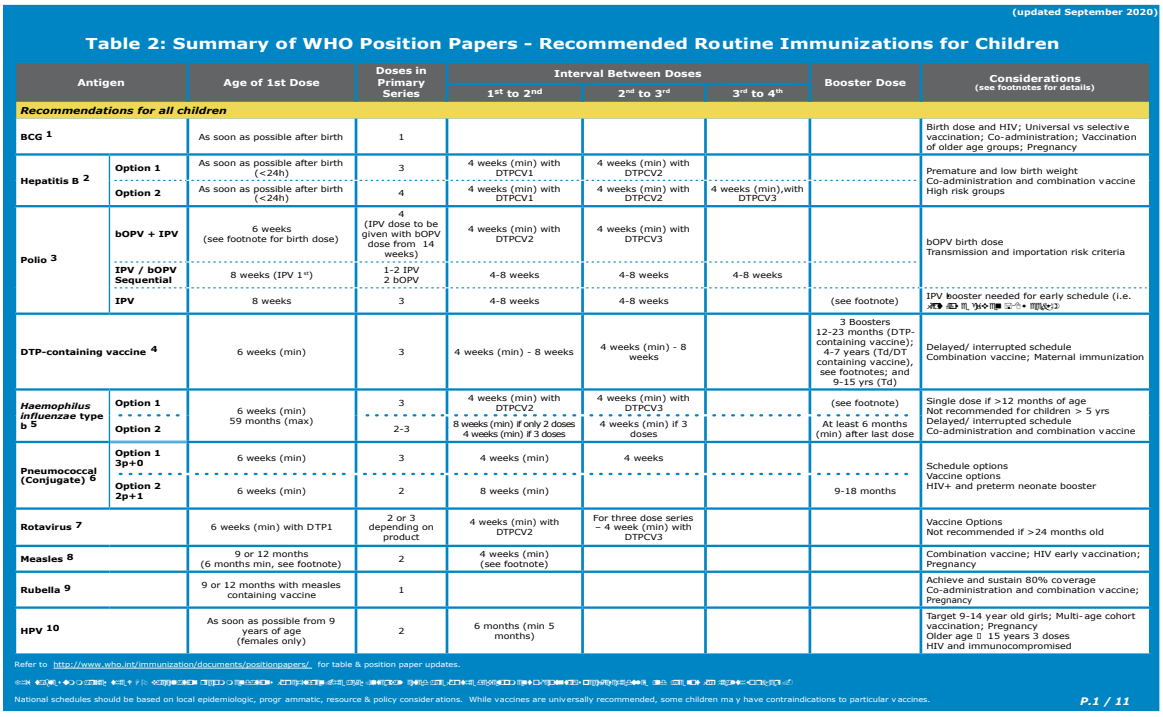
The goal of RI systems is to provide vaccinations against common childhood illnesses in a reliable and standard manner. In many places the goal is to transition away from immunization campaigns, which can quickly vaccinate a large number of children but are very costly with less long-term impact, to routine immunization systems that provide consistent long-term access to vaccination services at a lower cost.

The Global Vaccine Action Plan (GVAP) is a framework to create more equitable access to vaccines and is endorsed by 194 members of the World Health Assembly (WHA)[17]. The decade of 2010-2020 was proclaimed the "decade of vaccines" by GVAP.

Routine immunization has suffered from a public image crisis because routine is considered unimportant and "business as usual" versus being framed as a public health emergency like polio eradication or measles elimination[17]. Proponents of routine immunization strengthening struggle with the necessity for long-term investment, short political cycles, and measurable indicators for success[17]. A key component to reaching routine immunization goals is to strengthen the routine immunization services by strengthening the health system as a whole[17]. Having a strong routine

immunization system allows for the successful introduction of new vaccines and the continuation of past lifesaving gains made via mass immunization campaigns[17].

Figure 3: WHO Recommended Routine Immunizations for Children[18]



(updated September 2020)

Table 2: Summary of WHO Position Papers - Recommended Routine Immunizations for Children

Antigen		Age of 1st Dose	Doses in Primary Series	Interval Between Doses: 1st to 2nd	Interval Between Doses: 2nd to 3rd	Interval Between Doses: 3rd to 4th	Booster Dose	Considerations (see footnotes for details)
Recommendations for all children								
BCG [1]		As soon as possible after birth	1					Birth dose and HIV; Universal vs selective vaccination; Co-administration; Vaccination of older age groups; Pregnancy
Hepatitis B [2]	Option 1	As soon as possible after birth (<24h)	3	4 weeks (min) with DTPCV1	4 weeks (min) with DTPCV2			Premature and low birth weight Co-administration and combination vaccine High risk groups
	Option 2	As soon as possible after birth (<24h)	4	4 weeks (min) with DTPCV1	4 weeks (min) with DTPCV2	4 weeks (min),with DTPCV3		
Polio [3]	bOPV + IPV	6 weeks (see footnote for birth dose)	4 (IPV dose to be given with bOPV dose from 14 weeks)	4 weeks (min) with DTPCV2	4 weeks (min) with DTPCV3			bOPV birth dose Transmission and importation risk criteria
	IPV / bOPV Sequential	8 weeks (IPV 1st)	1-2 IPV 2 bOPV	4-8 weeks	4-8 weeks	4-8 weeks		
	IPV	8 weeks	3	4-8 weeks	4-8 weeks		(see footnote)	IPV booster needed for early schedule (i.e. [illegible])
DTP-containing vaccine [4]		6 weeks (min)	3	4 weeks (min) - 8 weeks	4 weeks (min) - 8 weeks		3 Boosters 12-23 months (DTP-containing vaccine); 4-7 years (Td/DT containing vaccine), see footnotes; and 9-15 yrs (Td)	Delayed/ interrupted schedule Combination vaccine; Maternal immunization
Haemophilus influenzae type b [5]	Option 1	6 weeks (min) 59 months (max)	3	4 weeks (min) with DTPCV2	4 weeks (min) with DTPCV3		(see footnote)	Single dose if >12 months of age Not recommended for children > 5 yrs Delayed/ interrupted schedule Co-administration and combination vaccine
	Option 2		2-3	8 weeks (min) if only 2 doses 4 weeks (min) if 3 doses	4 weeks (min) if 3 doses		At least 6 months (min) after last dose	
Pneumococcal (Conjugate) [6]	Option 1 3p+0	6 weeks (min)	3	4 weeks (min)	4 weeks			Schedule options Vaccine options HIV+ and preterm neonate booster
	Option 2 2p+1	6 weeks (min)	2	8 weeks (min)			9-18 months	
Rotavirus [7]		6 weeks (min) with DTP1	2 or 3 depending on product	4 weeks (min) with DTPCV2	For three dose series – 4 week (min) with DTPCV3			Vaccine Options Not recommended if >24 months old
Measles [8]		9 or 12 months (6 months min, see footnote)	2	4 weeks (min) (see footnote)				Combination vaccine; HIV early vaccination; Pregnancy
Rubella [9]		9 or 12 months with measles containing vaccine	1					Achieve and sustain 80% coverage Co-administration and combination vaccine; Pregnancy
HPV [10]		As soon as possible from 9 years of age (females only)	2	6 months (min 5 months)				Target 9-14 year old girls; Multi-age cohort vaccination; Pregnancy Older age ≥ 15 years 3 doses HIV and immunocompromised

Refer to http://www.who.int/immunization/documents/positionpapers/ for table & position paper updates.

[illegible]

National schedules should be based on local epidemiologic, progr ammatic, resource & policy consider ations. While vaccines are universally recommended, some children ma y have contraindications to particular v accines.

P.1 / 11

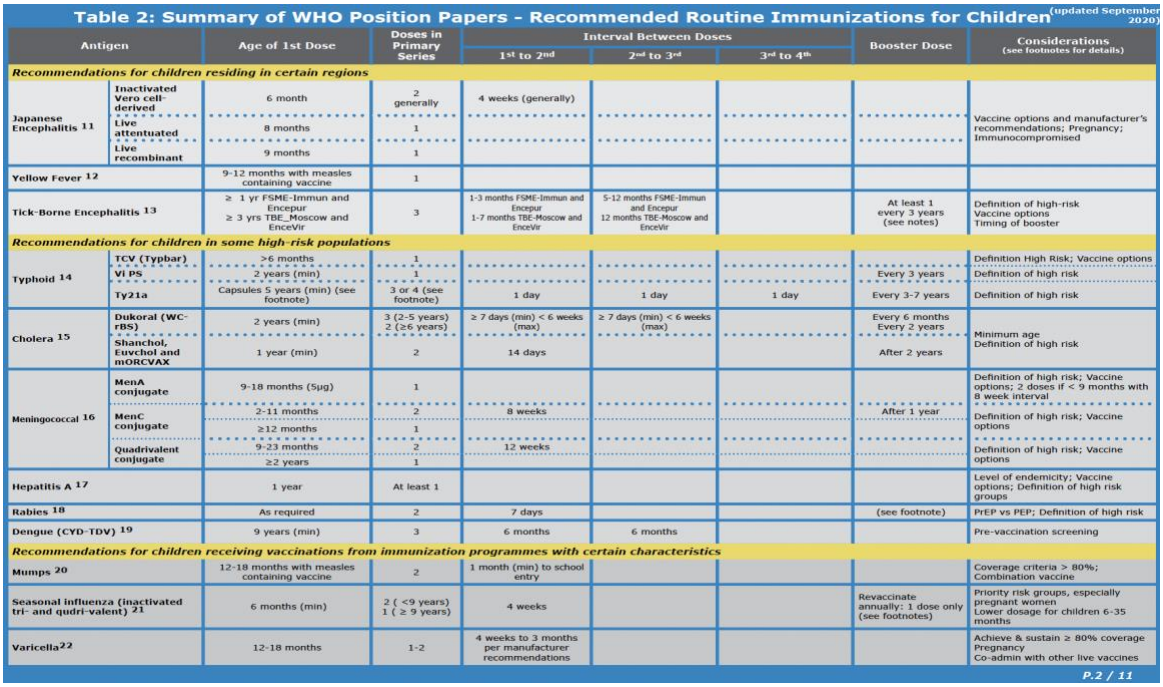


Table 2: Summary of WHO Position Papers - Recommended Routine Immunizations for Children (updated September 2020)

Antigen		Age of 1st Dose	Doses in Primary Series	Interval Between Doses: 1st to 2nd	Interval Between Doses: 2nd to 3rd	Interval Between Doses: 3rd to 4th	Booster Dose	Considerations (see footnotes for details)
Recommendations for children residing in certain regions								
Japanese Encephalitis [11]	Inactivated Vero cell-derived	6 month	2 generally	4 weeks (generally)				Vaccine options and manufacturer's recommendations; Pregnancy; Immunocompromised
	Live attentuated	8 months	1					
	Live recombinant	9 months	1					
Yellow Fever [12]		9-12 months with measles containing vaccine	1					
Tick-Borne Encephalitis [13]		≥ 1 yr FSME-Immun and Encepur ≥ 3 yrs TBE_Moscow and EnceVir	3	1-3 months FSME-Immun and Encepur 1-7 months TBE-Moscow and EnceVir	5-12 months FSME-Immun and Encepur 12 months TBE-Moscow and EnceVir		At least 1 every 3 years (see notes)	Definition of high-risk Vaccine options Timing of booster
Recommendations for children in some high-risk populations								
Typhoid [14]	TCV (Typbar)	>6 months	1					Definition High Risk; Vaccine options
	Vi PS	2 years (min)	1				Every 3 years	Definition of high risk
	Ty21a	Capsules 5 years (min) (see footnote)	3 or 4 (see footnote)	1 day	1 day	1 day	Every 3-7 years	Definition of high risk
Cholera [15]	Dukoral (WC-rBS)	2 years (min)	3 (2-5 years) 2 (≥6 years)	≥ 7 days (min) < 6 weeks (max)	≥ 7 days (min) < 6 weeks (max)		Every 6 months Every 2 years	Minimum age Definition of high risk
	Shanchol, Euvchol and mORCVAX	1 year (min)	2	14 days			After 2 years	
Meningococcal [16]	MenA conjugate	9-18 months (5µg)	1					Definition of high risk; Vaccine options; 2 doses if < 9 months with 8 week interval
	MenC conjugate	2-11 months	2	8 weeks			After 1 year	Definition of high risk; Vaccine options
		≥12 months	1					
	Quadrivalent conjugate	9-23 months	2	12 weeks				Definition of high risk; Vaccine options
		≥2 years	1					
Hepatitis A [17]		1 year	At least 1					Level of endemicity; Vaccine options; Definition of high risk groups
Rabies [18]		As required	2	7 days			(see footnote)	PrEP vs PEP; Definition of high risk
Dengue (CYD-TDV) [19]		9 years (min)	3	6 months	6 months			Pre-vaccination screening
Recommendations for children receiving vaccinations from immunization programmes with certain characteristics								
Mumps [20]		12-18 months with measles containing vaccine	2	1 month (min) to school entry				Coverage criteria > 80%; Combination vaccine
Seasonal influenza (inactivated tri- and qudri-valent) [21]		6 months (min)	2 (<9 years) 1 (≥ 9 years)	4 weeks			Revaccinate annually: 1 dose only (see footnotes)	Priority risk groups, especially pregnant women Lower dosage for children 6-35 months
Varicella[22]		12-18 months	1-2	4 weeks to 3 months per manufacturer recommendations				Achieve & sustain ≥ 80% coverage Pregnancy Co-admin with other live vaccines

P.2 / 11

1.3 THE EXPANDED PROGRAMME ON IMMUNIZATION IN DRC

Expanded Program on Immunization (EPI) in the DRC was established by the World Health Organization (WHO) in 1974 as a response to the Smallpox eradiation campaigns, to embed routine vaccinations within the health system[19]. The EPI was developed to expand child access to 6 lifesaving vaccines: tuberculosis, polio, diphtheria, tetanus, pertussis, and measles[19]. The foundation of the EPI created an official guideline to act as a framework to build up immunization programs around the world. The success of the EPI program has been clear with coverage rates for dose 3 of Diphtheria, Tetanus and Pertussis (DTP) containing vaccine rising from 5% in 1974 to over 50% by the late 80's[19].

Within the DRC, the EPI is a division within the Ministry of Health (MoH) and manages the Congolese routine immunization system. There are currently 8 vaccines, to protect against 11 vaccine preventable disease, for infants under 12 months included in the routine immunization schedule for DRC, with the 8th being the rotavirus vaccine that was introduced throughout the country in 2020[20](Table 1). While administrative coverage have all shown annual vaccination coverage rates over 80% since 2007, the 2013-2014 Demographic Health Survey (DHS) reported a complete vaccination coverage rate of about 45% in children 12-23 months and the 2017-2018 MICS found that only 35% of children 12-23 months were considered completely vaccinated[11,21](Figure 4). This represented a potential significant drop in complete vaccination coverage between 2013-14 and 2017-18.

In order to determine when to introduce a new vaccine the EPI must work with the MOH, Congolese government and external partners to determine if the existing routine immunization system is strong enough with a robust accountability system, motivated workforce, sufficient

logistical support, monitoring capacity for adverse events, high quality surveillance and financially sustainable[22].

Figure 4: MICS 2017-18 Full Vaccination Coverage in DRC[11]

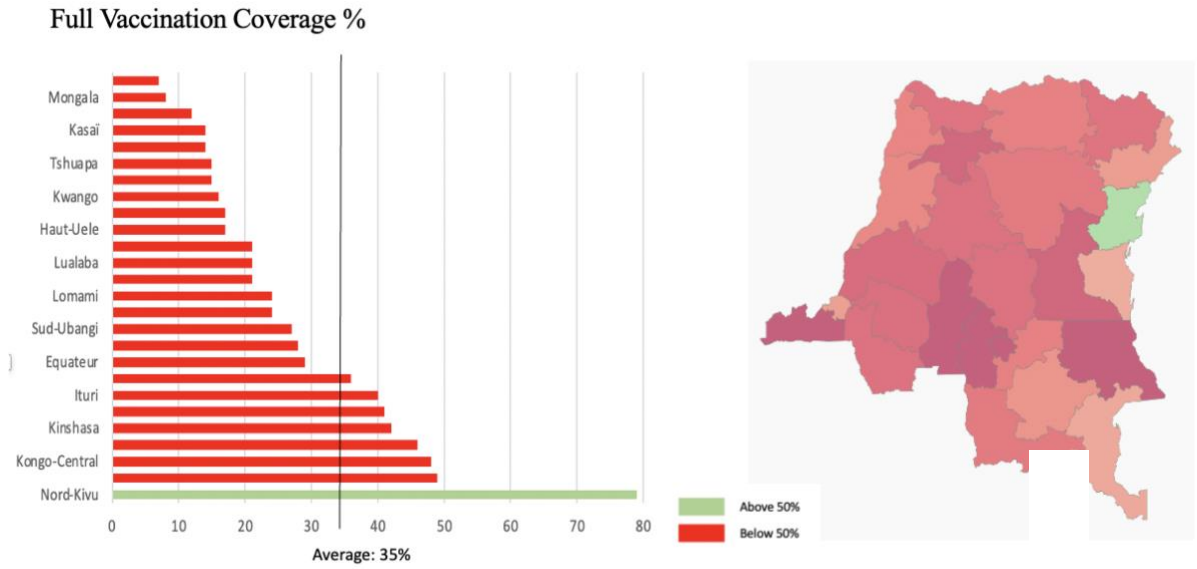


Table 1: DRC Routine Immunization Schedule[23]

Routine Immunization Schedule in the Democratic Republic of the Congo		
Vaccine	**Description**	**Schedule**
BCG	Bacillus Calmette–Guérin vaccine	Birth
Penta	Diphtheria, Tetanus, Pertussis, Haemophilus Influenzae Type B, and Hepatitis B Vaccine	6, 10, 14 weeks
OPV	Oral Polio Vaccine	6, 10, 14 weeks
Pneumo	Pneumococcal Conjugate Vaccine	6, 10, 14 weeks
IPV	Inactivated Polio Vaccine	14 weeks
Measles	Measles Vaccine	9 months
YF	Yellow Fever Vaccine	9 months
Rota	Rotavirus Vaccine	6, 10, 14 weeks

1.4 MASHAKO PLAN BACKGROUND AND IMPLEMENTATION

In response to the decrease in full vaccination coverage across provinces, the Congolese government and the EPI worked in conjunction with key partners, Gavi, The Vaccine Alliance (GAVI) WHO, UNICEF, Village Reach, Acasus, The Bill & Melinda Gates Foundation (BMGF), PATH, World Bank and USAID, to develop an emergency strategy to revitalize the RI system. This group identified 5 key areas for improvement in the DRC RI system. These areas were vaccine availability, equality of vaccination services, data quality and management, monitoring and evaluation programs and workforce development. In order to strengthen these 5 areas, the partners sought to develop a plan that focused on structural issues at lower levels of the system and created clear guidelines with tangible steps and monitorable indicators that could be implemented within 18 months of implementation[23]. This plan included significant political will from the Congolese government, restructuring of existing resources. For RI services and the support of global partners. The Mashako Plan is a prime example of a significant investment by government and global partners to strengthen the routine immunization system, that has a tangible short and long-term indicators for success. The 5 goals of the final Mashako Plan are as follows:

1. Immunizations: increase the number completed vaccination sessions by 20% with 18 months of implementation

2. Supervision: monthly inspection of immunization activities in health zones, health areas and vaccine storage sites and facilities by inspectors

3. Monitoring and evaluation: monthly monitoring of data results of vital indicators such as cold chain, vaccine availability and held sessions

4. Stockout reduction/ vaccine availability: to reduce stockouts by 80% at health facilities within 18 months of implementation

5. Coordination and financing: monthly meeting to discuss implementation challenges and ensure proper funding allocation

In July of 2018 workshops were held at national and sub-national levels to determine the primary goals and activities of the Mashako Plan and to establish priority provinces for implementation. Coordination teams were established in September of 2018, and the Mashako Plan was officially launched in October of 2019. The Plan Mashako is being rolled out in three phases. Phase 1 included 9 provinces, October to December 2019: Kasai, Haut Katanga, Ituri, Mongala, Kwilu, Tanganyika, Kinshasa, Tshuapa and Haut Lomami. These initial 9 provinces were selected because of vulnerability, high population density, VPD outbreaks and low vaccination coverage. These 9 provinces make up 40% of the population and 45% of unvaccinated children according to the most recent DHS survey[24].

Phase 2 includes an additional 9 provinces, Kongo Central, Kasai Oriental, Kwango, Kasai Central, Lomami, Maniema, South Kivu, Sankuru and Tshopo, that were scheduled for launches throughout the first half of 2020, however, rollout was paused from March-September 2020 due to COVID-19, thus these 9 provinces were launched in Q4 of 2020 (Figure 5). Five provinces were delayed, due to the COVID-19 pandemic, until 2021 and the final 3 provinces implemented the Mashako Plan activities in the second half of 2022 (Figure 5).

Figure 5: Mashako Plan Policy Implementation Timeline

Figure 5a. Planned

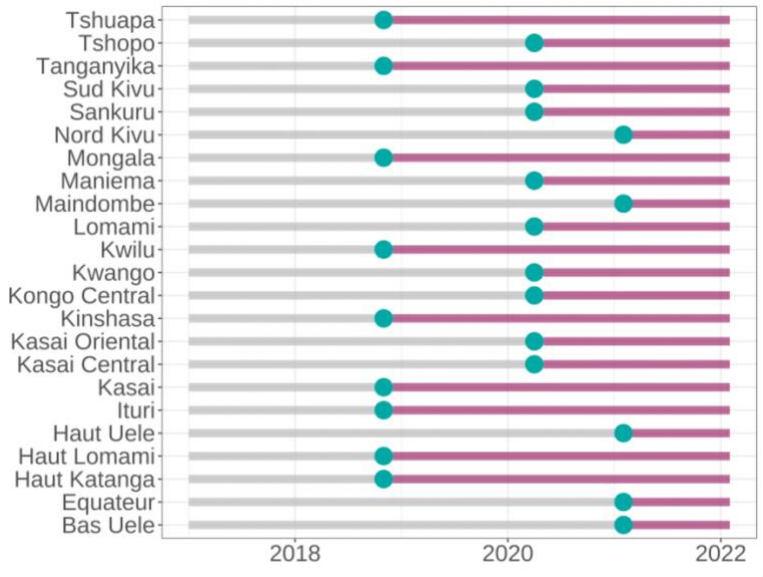
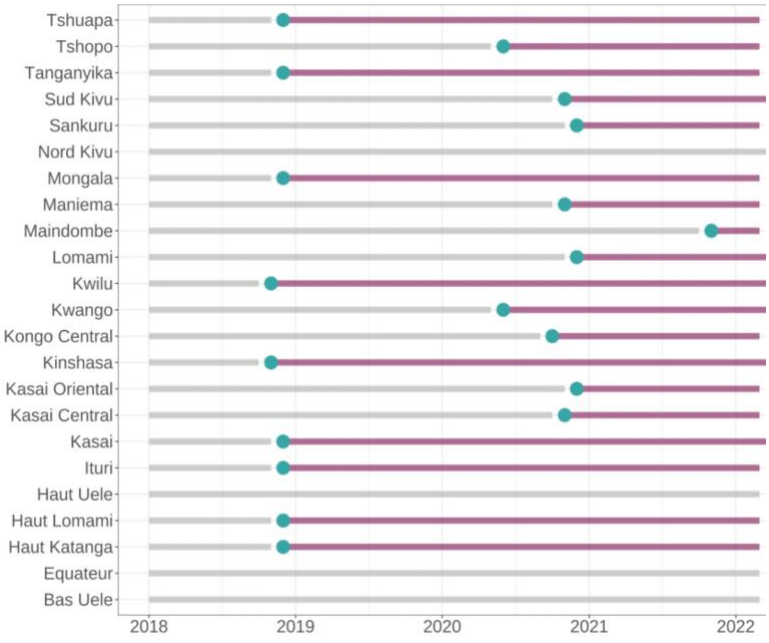


Figure 5b. Implemented (first reported mobile supervision visit)



1.5 THESIS RATIONALE

The Mashako Plan has been received as a very important policy measure in the DRC. This platform addresses many different aspects of the immunization system in a straightforward user-friendly way which engages all levels of the vaccination structure, including the end users, in the routine immunization system; it is a collaborative effort between the Congolese government, Gavi, the vaccine alliance (Gavi) and many other global partners. If successful, this platform to strengthen RI systems could transform the way RI systems are supported, by demonstrating the advantage of straightforward yet innovative techniques such as political engagement, sub-national financial management, mobile monitoring and evaluation and vaccine logistics.

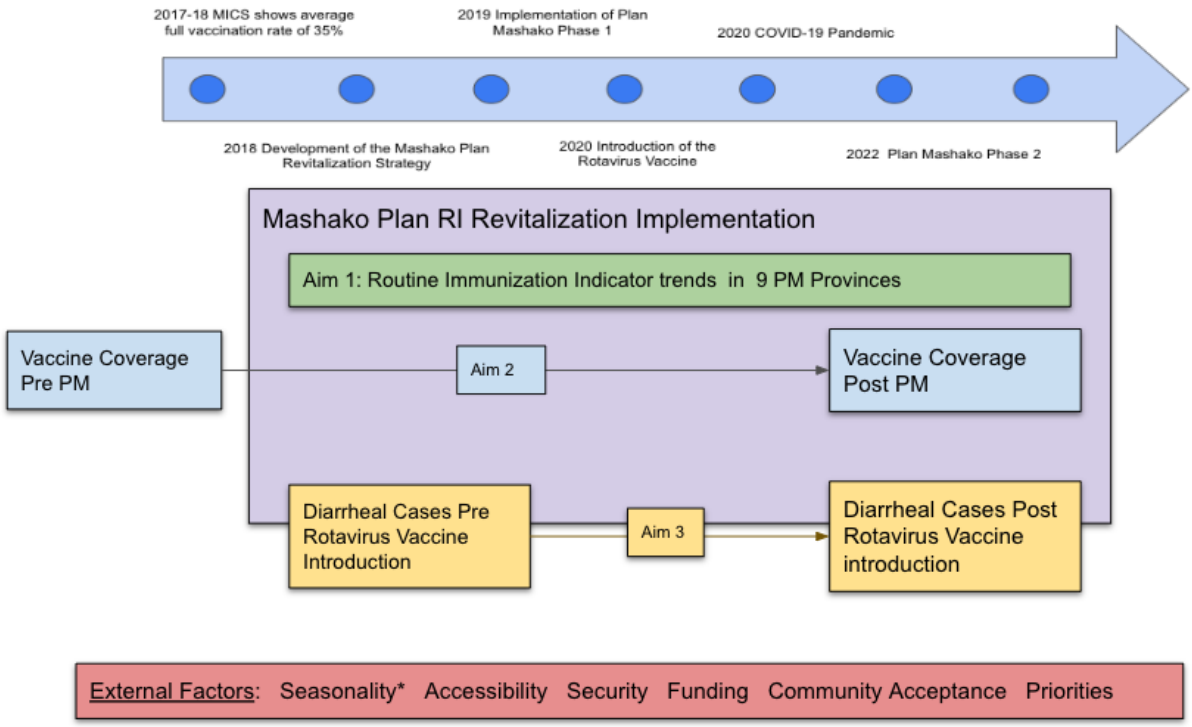
Up until this point very little has been officially published about the Mashako Plan and outcomes from the implementation of these strategies. This dissertation aims to understand the role of the Mashako Plan on vaccination doses administered, the trends of process indicators among Mashako Plan provinces and how the Mashako Plan strengthening activities impact new vaccine introduction (Table 2). Over the course of the implementation of the Mashako Plan several events such as the COVID-19 pandemic occurred, these are documented along with the timing of data collected in the diagram provided (Figure 6).

Table 2: Aims Overview

Aim	Data Source	Time Frame
Aim 1: Identify trends in process indicators of the RI system in the initial 9 PM provinces, January 2019-December 2021 (Chapter 2)	EPI Mobile Supervision Data	January 2019-December 2021
Aim 2: Assess the impact of Plan Mashako implementation on vaccine doses administered (Chapter 3)	DHIS2	January 2017-January 2021
Aim 3: Assess the effect of rotavirus vaccine on childhood diarrheal disease incidence, comparing Plan Mashako to Non-Plan Mashako provinces (Chapter 4)	DHIS2	January 2019-December 2021

Chapter 2 of this dissertation aims to look into the trends seen in RI process indicators after the implementation of the Mashako plan to revitalize the routine immunization system. Chapter 3 uses an interrupted time series analysis to look into the impact of the Mashako plan policy on vaccine doses administered. The third dose of the pentavalent vaccine series, administered at 14 weeks in the DRC RI system is the primary outcome of interest, however the first dose of this series and the measles vaccine were also evaluated as secondary outcomes. The 4th chapter looks into new vaccine introduction into the RI system in DRC. New vaccine introduction is not something that has been evaluated before in the DRC and this chapter attempts to use administrative data to evaluate the impact of the rotavirus vaccine introduction and determine if there are any differences in outcomes between provinces that had received the Mashako revitalization policy and those that had not.

Figure 6: Dissertation Schematic



1.6 DATA SOURCES

District Health Information Software 2 (DHIS2)

The District Health Information Software 2 (DHIS2) is an open-source web-based platform and the world's largest Health Management Information System (HMIS) launched in 2009 and data is collected at the health facility level[25]. The DHIS2 is used in over 100 counties, supporting 2.4 billion people; of those 100 countries 73 are low- and middle-income countries (LMICs). The DHIS2 was created through a global collaboration of 13 countries and is managed by the Health Information Systems Program (HISP) at the University of Oslo[25]. Variables included in the DHIS2 include all indicators related to health systems management and include population estimates,

births, deaths, disease surveillance, facility operations, stock management, facilities management, consultations, malaria indicators, and vaccination data. The system is also designed to collect specific program information such as HIV indicators, nutrition program indicators and systems strengthening indicators as requested by national programs and partners.

Sampling frame: Data is collected from all 26 provinces, 519 health zones, and 8,971 health areas. There are over 17,000 health facilities that report to the DHIS2 and other health systems platforms in the DRC monthly. Typically, in each health zone, there is one general hospital and there are between 10-20 health areas. Within these health areas there is typically a health center, and, in some cases, a smaller remote facility called a health post and depending on population size, there may be multiple health centers. Information may be missing from people that seek services outside of the government run health system, such as from private facilities or traditional healers as these facilities may not be incorporated into the DHIS2 platform; these practitioners could be included if they work at local health facilities, but this is not well documented in the system. Additionally, data may be delayed depending on availability of internet for entering data. It is also possible that multiple facilities could aggregate data to complete just one monthly form.

EPI Mobile Supervision Data

Introduced in January 2019 as a key component of the Mashako Plan, the EPI Mobile Supervision system provides a mobile platform for routine monitoring of health facilities on a monthly basis. Data is collected via a mobile survey application downloaded on provided cell phones. These cell phones have the ability to collect survey data without a cellular or internet connection and results are uploaded once connected to the internet. The system is set up that every health area should have at least one facility within it visited each month. The choice of the facility (health center, health post, or hospital) visited within the health area is the choice of the supervisor, thus the

denominator for completeness of this variable is total number of health areas and not total number of facilities. Thus, it is possible that health areas could have multiple facilities visited during the month, but only one visit (the last one in the month) will be used for supervision reports.

Sampling Frame: In 2019, 9 provinces implemented this monitoring system, in 2020 9 additional provinces were added and in 2021 the final 8 provinces were included. Data is available by health area for individual health facilities, with each health area recording data from one health facility each month.

Chapter 2: Understanding Routine Immunization Patterns in 9 "Mashako" Provinces: Insights from EPI Mobile Supervision in the Democratic Republic of the Congo

2.1 ABSTRACT

BACKGROUND

Full routine immunization (RI) coverage in the Democratic Republic of the Congo (DRC) has been below 50% respectively, 45% and 35% based on the national surveys conducted in 2013-2014 (DHS) and 2017-2018 (MICS), respectively [24,26]. In 2018, the government of the DRC with support from global partners committed to revitalizing the routine immunization system through the introduction of a cross-sectoral program called the Mashako Plan. This program focused on systemic changes that could improve accessibility of routine immunization services for the Congolese population. The systemic interventions that strengthen accessibility in a routine immunization system include vaccine availability, equality of vaccination services, data quality and management, and evaluation programs and workforce development. This is a descriptive analysis of process indicators for RI and demonstrates the resilience of the RI system in DRC to large global events such as the COVID-19 pandemic.

METHODS

The data used in these analyses come from monthly cross-sectional Expanded Programme for Immunization (EPI) mobile supervision surveys completed in the nine initial Mashako provinces. Monitoring surveys were collected from at least one facility in each health area of the selected provinces every month from January 2019 to December 2021. The questionnaire was developed by the DRC EPI in collaboration with a consulting partner organization and administered on cell phones by identified supervisors. In order to evaluate the trends over time for all process indicators, the monthly means for immunization sessions, refrigerators, functional refrigerators, health areas

(HA) visited, and pentavalent, BCG, measles and rotavirus vaccines were plotted over time. Simple linear regressions were also run, regressing the indicators against time to determine if there was a positive trend.

RESULTS

From the plotted trends of process indicators, the mean number of immunization sessions held per health facility in each province remains fairly consistent over time, regardless of the COVID-19 pandemic. Similarly, we see increases in doses of vaccines available in health facilities over time with no impact from the COVID-19 pandemic. The availability and functionality of refrigerators in facilities remains constant and number of health areas supervised remains constant over time with no impact observed from the COVID-19 pandemic and related lockdowns. Interestingly we do see drops in Health Area supervision activities later in 2021 which corresponds with internal healthcare worker strikes in DRC.

CONCLUSION

EPI mobile supervision data provides a unique source of information to monitor sub-national trends in RI services and accessibility in DRC. These results demonstrate a system that seems resilient to global trends but sensitive to internal events.

2.2 BACKGROUND

The Democratic Republic of the Congo (DRC) has faced challenges in providing adequate routine immunization (RI) services to its population, as evidenced by the results of the Demographic and Health Survey (DHS) 2013-2014 and Multiple Indicator Cluster Survey (MICS) 2017-2018. In response to low vaccination coverage rates, the DRC government, in partnership with global partners, launched the Mashako Plan in late 2018, a comprehensive program aimed at revitalizing the country's RI system.

The Mashako Plan was meant to respond to low vaccination coverage rates by targeting five key aspects to strengthen the routine immunization system. These five aspects include vaccine availability, equity of vaccination services, data quality and management, monitoring and evaluation programs and workforce development. The Mashako Plan put policies in place for all of these aspects to strengthen the accessibility of the RI system. By improving standards and policy around vaccine delivery and number of immunizations sessions held, they planned to improve availability of vaccines and vaccine equity for communities. A policy was put in place that aimed to improve monitoring of the routine immunization system. By increasing monitoring of the RI system, they hope to more quickly identify challenges and create a more resilient structure with the ability to adapt to extreme events[27]. In recent years, resilience of a health system has become a key framework when thinking about global health; in a health system literature review by Biddle et al. infectious disease outbreaks were the most commonly addressed challenge when evaluating the resilience of a system and they identified key factors to improve system resilience including effective communication, sufficient resources, robust surveillance and early warning systems, emergency planning and ongoing training[28]. By implementing the Mashako Plan policy, the MOH and partners hoped to create a more resilient routine immunization system byt strengthening many

of these key aspects. If implemented correctly, these systems should be more resilient or at least adaptive to catastrophic events[27]. Monitoring systems provides real-time information to nimbly make decisions in the face of emergencies that could otherwise derail standard health delivery systems. As part of the Mashako Plan implementation, EPI Mobile Supervision surveys were implemented to provide monthly feedback to the EPI program about the accessibility and functionality of the RI system.

The global Coronavirus pandemic is this type of catastrophic event that impacted health systems across the globe. The COVID-19 pandemic cost the world over 6 million lives and disrupted the entire fabric of our societies[29]. The WHO estimates that the number of unvaccinated for routine immunizations children increased by 3.4 million in 2020 and global vaccine coverage dropped from 86% to 83% due to the pandemic [30]. In the DRC, the impact of COVID-19 has not been as obvious as in other parts of the world. As of late 2022, the WHO reports that there are just over 95,000 confirmed cases of COVID-19 and just under 1,500 deaths[31] (Figure 1). These numbers are most likely underestimates given the availability of testing and reporting. Despite potential for underestimation these numbers are still quite low given the size of the population in DRC. With the median age in the DRC being 17 years and the age distribution of the population, it is possible that many cases go undetected in the population[32].

Despite the lower-than-expected cases and deaths in the DRC due to COVID-19, preliminary results from the Kinshasa School of Public Health vaccine coverage survey in 23 of the 26 provinces show that there is a small drop in vaccine coverage in 2020 for younger children compared to older children who would have likely completed their vaccination schedule before COVID-19, or at least already started vaccination compared to those 6-11 months[33]. This differs from the results of the Hategeka et al. study that looked at the impact of COVID-19 on health

services and did not find any impact on vaccinations in the administrative data, however, this was just one of many variables explored, but not in depth[34]. In this study we describe the trends of RI system process indicators from 2019 until 2021, in the initial 9 Mashako Plan provinces. We hypothesized that process indicators that are dependent on a global supply chain or impacted by COVID-19 lockdown policy measures would increase before March 2020 and then decrease after the start of the pandemic but that cold chain functionality would not be impacted. The EPI Mobile Supervision can provide insight into the accessibility of the RI system in DRC which compliments the utilization data provided from outcome based data sources such as administrative data that can help provide a full picture of the condition of the RI system.

2.3 METHODS

Data Source

This study uses data from the EPI Mobile Supervision tool to identify trends in process indicators for the vaccination system. The EPI Mobile Supervision tool is a survey conducted at monthly supervision visits in at least one health facility in each health area of the health zone. Health zones are typically made up of smaller catchment areas – health areas, that then serve the population and typically have at least one, but sometimes additional facilitates, depending on population and area of the health area. The survey data collects process indicators at the health area level, including supervision visits, cold chain function, vaccination sessions, and vaccine stock levels. The data used for these analyses was collected from January 2019 to December 2021 for the 9 initial Mashako Plan provinces. The questionnaire was developed by the DRC EPI in collaboration with a consulting partner organization and administered on cell phones by identified supervisors. A copy of the EPI Mobile Supervision Survey is included in the supplemental materials document 1.

Table 1 provides key information about the study sample, including the number of unique health areas monitored and the total number of observations analyzed in each of the 9 provinces.

Indicators

The process indicators that we evaluated in this study were mean number of doses of Pentavalent, Measles, Bacille Calmette-Guérin (BCG) and Rotavirus vaccine available, mean number of monthly immunization sessions, percentage of facilities with refrigerators, percentage of facility refrigerators functioning, and the number of health areas supervised each month.

Statistical Analyses

The EPI Mobile Supervision Data was received as excel files that were merged together using Stata and then imported into R for further cleaning and analyses. For these analyses the data was limited to only the initial 9 Mashako Plan provinces because these provinces had the most complete data with at least 34 months of supervision visits recorded. Means were generated for the number of immunization session held each month as well as the doses of vaccines available. For outcomes of interest with continuous values, outlier observations outside of 3 standard deviations of the mean were excluded. The percentage of facilities with refrigerators and the percentage of facilities with working refrigerators were plotted over time as well as the total number of health areas supervised each month in each province.

All indicators were plotted over time and linear tests for trend were performed regressing the indicators on time to determine if there was an overall positive trend.

Ethics

This activity was determined to be exempt from IRB (IRB#22-001553) at UCLA and the data is available from the MoH in DRC upon request.

2.4 RESULTS

Supervision Visits

When looking at the number of health areas supervised per month in each province, we see an increase at the beginning of the implementation of supervision visits and then a general flattening of the trends in the middle (Figure 2). Haut Lomami, Kasai, Kinshasa and Tshuapa appear to have a small drop in the number of unique HA supervised for one month in March of 2020 with 84%, 78%, 75% and 51% of health areas supervised respectively. In Ituri there is a small 3-month dip at the same time with the percent of HA being supervised ranging from 72-79% of the total health areas in the province over those three months. All other provinces do not see noticeable changes in the number of unique health areas supervised (Supplementary Table 1). In May of 2021, several provinces experienced a sharp drop in health areas supervised including Haut Katanga, Haut Lomami, Kasai, Kinshasa, Kwilu and Tanganyika, they reported 48%, 60%, 63%, 51%, 76%, and 57% of HA were supervised respectively. The provinces that had a minimal change in the number of HAs supervised in 2021 were Mongala, Ituri and Tshuapa.

Immunization Sessions

The plots of mean immunization sessions per month for each province show generally the same trend of consistent immunization sessions (Figure 3). Haut Katanga, Haut Lomami and Kinshasa provinces had positive trends with the most immunization sessions per month on average with between 4 and 8 sessions a month, Kasai, Tanganyika, Tshuapa, and Mongala also saw positive trends reaching around 4 sessions a month and Ituri and Kwilu also saw positive trends but with around 2-3 of sessions a month.

Vaccine Stock

We have also plotted the stock of vaccine doses available with the sessions for pentavalent, measles, BCG and rotavirus. We see a generally positive trend for all antigens which is confirmed by linear regression tests for trend which all have a significant positive result (Figure 3 & Table 2). Pentavalent vaccine doses available increases significantly over time in Haut Lomami, Tanganyika and Kwilu, peaking at a mean number of doses of pentavalent vaccine available at 107, 158 and 135 respectively. It also increases in Mongala, peaking at 192 mean doses available, but drops back down to previous levels, 121 mean doses available, at the end of the time period. Kasai, Ituri and Haut Katanga have a more moderate positive trend over time, peaking at 68, 99 and 128 mean doses available respectively, Tshuapa has a negative trend, dropping to 55 mean doses available at the lowest point, which then rebounds up to a mean of 90 doses available, similar to the start and Kinshasa starts with a mean of 121 doses of pentavalent vaccine available and experiences small increases and decreases over time peaking at 156 doses available and dropping to 100 doses available to end with a mean of 116 doses available at the end of the observed time period. Despite the variations, the linear test for trend regressing pentavalent vaccine doses available on time gives an estimate of 1.6 (1.4, 1.9) indicating an overall positive trend (Table 2). For the rotavirus vaccine doses available, the plots all start out flat indicating 0 doses available before the vaccine was initially distributed, for the January 2020 vaccine introduction. We see the rotavirus vaccine doses available quickly increase to match the trend of the Pentavalent vaccine. We do see a significant drop in doses of BCG vaccine available which indicates stock outs of this vaccine in mid- 2021, especially in Mongala, Tanganyika, Kwilu, Kinshasa, Haut Lomami, and Tanganyika, which drop to 81, 58, 49, 44, 26 and 58 mean doses of BCG vaccine available respectively. This aligns with documented stockouts of BCG from May to July of 2021[35]. While there is variation, the linear test for trend regressing BCG vaccine doses available on time gives

an estimate of 0.376 (0.195, 0.557) indicating an overall positive trend (Table 2). For the measles vaccine, we see positive trends for Mongala and Tanganyika, peaking at 132 and 155 mean doses of measles vaccine available respectively, the other provinces Haut Katanga, Haut Lomami, Ituri, Kasai, Kwilu, Kinshasa, Tshuapa have moderately positive trends, peaking at 64, 80, 55, 29, 77, 94 and 85 doses of measles vaccine available respectively. The linear test for trend regressing measles vaccine doses available on time gives an estimate of 0.891 (0.732, 1.050) indicating an overall positive trend (Table 2).

Cold Chain Functionality

In spite of concerns regarding disruptions to healthcare services during the COVID-19 pandemic, we observed no significant changes data for refrigerator access or functionality during the study period. The percentage of facilities with refrigerators were plotted over time and showed a generally flat or slightly positive trend in all provinces (Figure 4). Haut Lomami, Kwilu, Tshuapa, and Tanganyika showed a generally positive trend over time with Haut Lomami having a strong positive spike in late 2021, while the other five provinces remain consistent (Figure 4). The percentage of functioning refrigerators mimicked the number of total refrigerators almost exactly indicating that nearly all machines were functioning at the time of the supervision event, this remained true at the time of the COVID-19 pandemic.

2.5 DISCUSSION

A plethora of studies have shown varying impacts of the COVID-19 pandemic on routine immunization services globally. We find that there was minimal to no impact of the COVID-19 pandemic on the RI system process indicators evaluated. This study adds to previous research in DRC that demonstrates limited impacts of the COVID-19 pandemic on immunization services in DRC[34]. Three possible explanations for this minimal impact are: the existence of a functional

subnational immunization system, the limited impact (cases and deaths) of the pandemic in DRC, or that the routine immunization process indicators used in this study have limited sensitivity to detect changes. Research documenting the impact of COVID-19 on service utilization in DRC varies. An article currently in pre-print found that while initial impacts were not obvious longer-term utilization of health services has minimized since the start of the pandemic in March 2020 in DRC[36]. Another article that examines the impact of the COVID-19 pandemic in DRC on adverse birth outcomes suggests that the health system remained resilient to the pandemic, but more research is needed to determine why and how the system seems resilient to the global events[37].

A study by Shaikh et al. reviewed the global impact of the COVID-19 pandemic on BCG vaccination and, through modeling, estimates a 25% reduction in global BCG coverage due to the pandemic[38]. A systematic review of the impact of the COVID-19 pandemic on routine vaccination coverage in children found that the majority of studies identified a decline or delay in vaccination, however of the 21 studies reviewed, 2 found no change in vaccination rates and 3 found small increases in influenza vaccines only[39]. Another modeling study that based expected vaccination levels on historical trends from publicly available data (WUENIC estimates) suggests a 2.9% global drop in the third dose of DTP containing vaccine which would translate to a potential 15-year setback in RI gains, however a larger modeling study that estimated global disruptions due to COVID-19 by region estimated the lowest annual impact on vaccine delivery for sub-Saharan Africa which aligns with the minimal impact we see in our results (3.8% DTP3, 4.4%MCV1)[40, 41]. A study in Ecuador saw a significant drop in the number of vaccine doses delivered to facilities in 2020[42]. A study conducted only in Kinshasa, DRC at the beginning of COVID-19 saw specific changes in immunization services only in the neighborhood of Gombe (the business center of the city) and no overall impact to services in Kinshasa, indicating that any impacts may not be seen at

the provincial level or that only specific locations such as large business centers and international hubs of DRC would see changes[34].

When reviewing the trends of all process indicators we see clear increasing trends with minimal to no impact from COVID-19 in DRC. We see a drop in HA supervised mid-2021, specifically at month 29 which is May of 2021, which coincides with a healthcare worker strike that occurred in many provinces in late 2021, in which healthcare workers were protesting low wages/lack of payment for hours worked. With the introduction of the rotavirus vaccine into the system in 2020, we see a quick increase in the mean doses of vaccine available to match those of the pentavalent vaccine available. This is encouraging because these vaccines are both given at one, six, and 14 weeks so we would expect similar doses of these vaccines to be available. These results imply that our hypothesis that COVID-19 would impact the RI system process indicators that could be influenced by global supply chain and international travel restrictions may not have been as strong as anticipated or measurable within the context of the current system. The cold chain indicator is where we expect the least variability or influence from outside events, and this seems to hold true given the trends observed.

To the authors' knowledge, this is the first use of the EPI Mobile Supervision data to identify trends in routine immunization process indicators in DRC. A similar study that evaluated the impact of supportive supervision within the context of a program to strengthen routine immunization in India found that these activities supported improved cold chain and were strengthened by the support of the government to drive these RI strengthening activities[43]. A study in Pakistan that implemented a mobile data collection platform into their immunization program monitoring found the use of the application was generally well accepted and thought to be superior to manual tracking of indicators[44]. Overall, they found that the coordination of the EPI was

improved with the use of this mobile application, while the indicators and method of data collection varied from our methods in this study, it does align with our results of seeing a positive trend in immunization indicators using a mobile supervision tool[44].

The results of this study should be interpreted in light of its limitations. The identification of trends over time in the process indicators for the routine immunization system can provide insights in changes but cannot demonstrate any causal relationships between these trends and exposures. Because these process indicators are only recorded if the supervision visit happens, any missed visits due to factors such as COVID-19 shutdowns or strikes will have missing data for all other process indicators which means there may be issues with non-random missingness. Additionally, the EPI Mobile Supervision data was collected by assigned supervisors on cell phones from at least on health facility in every health area every month, therefore, we can only make inferences down to the health area level. This design means that not every facility is supervised every month and the facility determination is done by the supervisor. This data collection method has limitations because the data may not be longitudinal from each facility if there are multiple facilities in a health area and the selection of facilities is not randomized. Because facility selection is left to the discretion of the supervisor, it is possible that there may be some bias in facility selection (i.e. higher functioning facilities may be selected more often especially if lower functioning facilities are closed and therefore unavailable to be supervised). These data cannot provide any insight into utilization of the RI system, only availability and accessibility.

2.6 CONCLUSION

The findings from the EPI Mobile Supervision data can inform policymakers, program managers, and other stakeholders on the progress made in improving accessibility to RI services, as well as the ongoing challenges that need to be addressed. This study provides insight into how the RI

system in DRC has adapted and responded to global events, which may be valuable to other countries facing similar challenges. This study offers valuable perspective on the trends in RI process indicators in DRC and suggests that the impact of the COVID-19 pandemic on these indicators may have been minimal. Trends in process indicators contribute meaninful context into whether systems or behavioral aspects are driving vaccinations. Additionally, the EPI Mobile Supervision Data is a new source of data that has not had much analysis done with it, so this is an exciting opportunity to explore this data source and provide additional insight into the accessibility of the RI system. This data in conjunction with other data sources that provide details on RI system utilization can help form a more clear picture of the overall state of the RI system in DRC. Future research is needed to better understand the factors that may have contributed to the observed trends, and to identify strategies to strengthen RI system accessibility and improve vaccination coverage in DRC and other settings.

Tables and Figures

Figure 1. WHO COVID-19 Dashboard Results for DRC, 2020-2022[31]

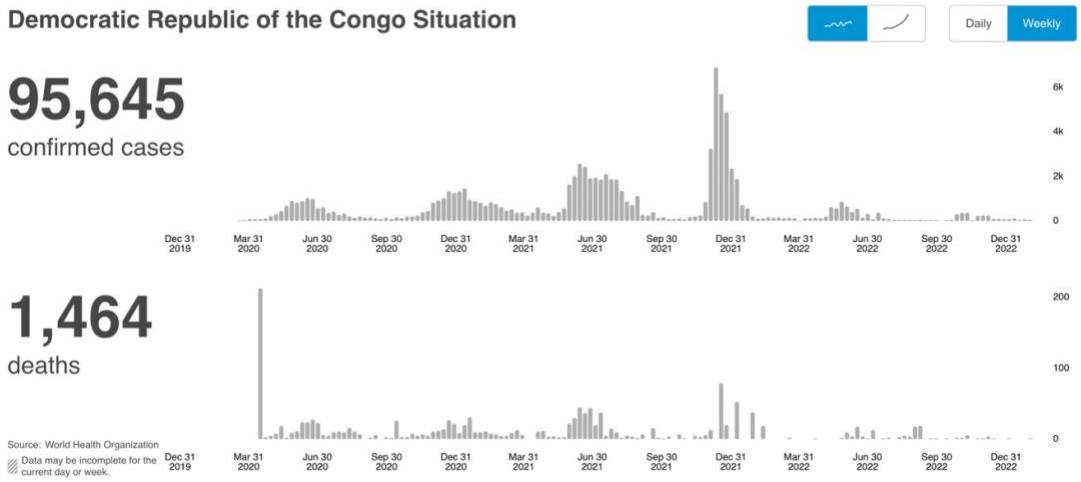


Table 1. EPI Mobile Supervision Data 9 Mashako Province Observations, Jan 2019-Dec 2021

Province	Unique Health Areas	Number of Observations
Haut Katanga	376	14120
Haut Lomami	323	10621
Ituri	568	16753
Kasai	393	12988
Kinshasa	380	13765
Kwilu	616	20891
Mongala	289	8982
Tanganyika	265	7655
Tshuapa	247	5895

Figure 2. Number of Health Areas Supervised per month

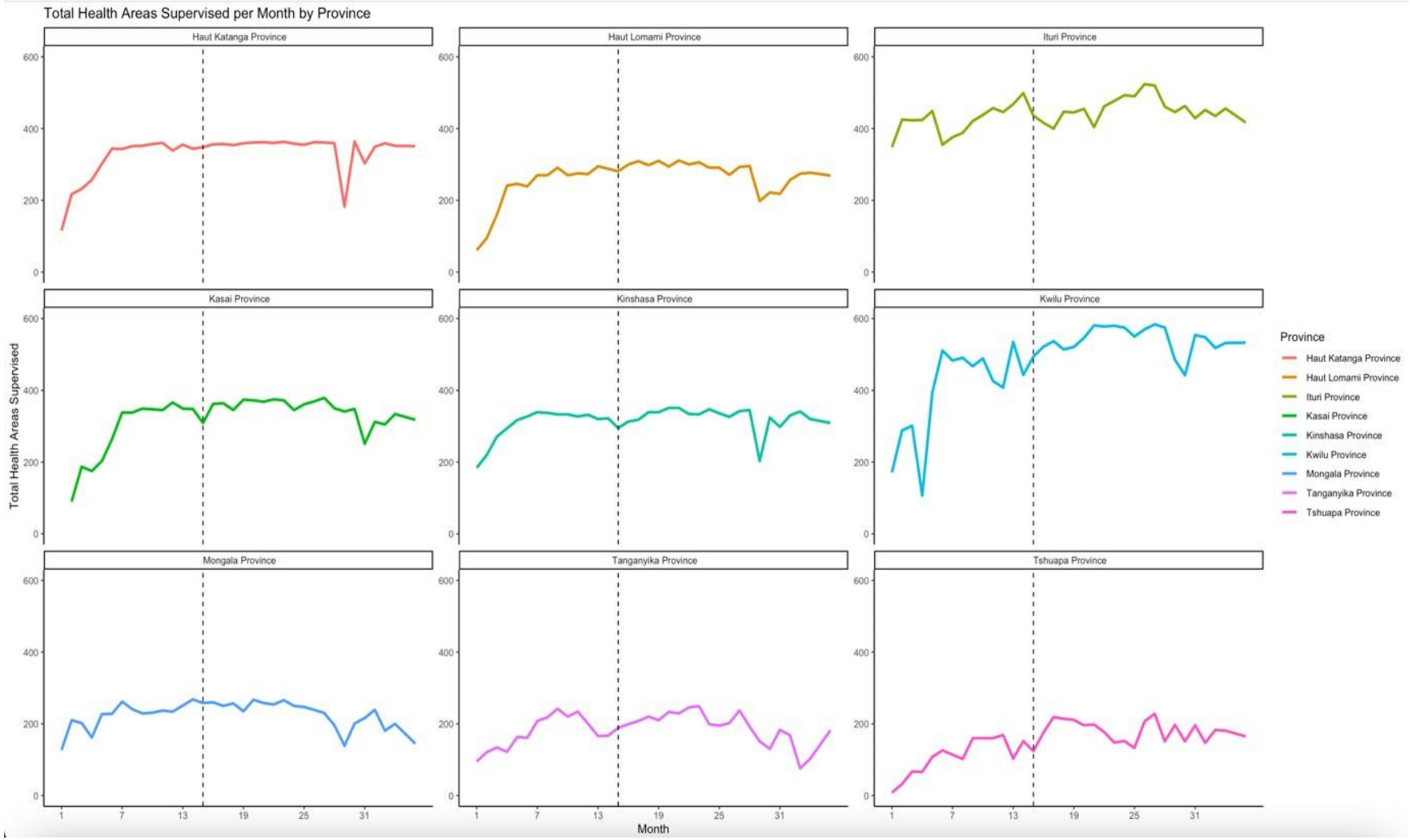


Figure 3. Mean Immunization Sessions plotted over time with trend lines of vaccine doses

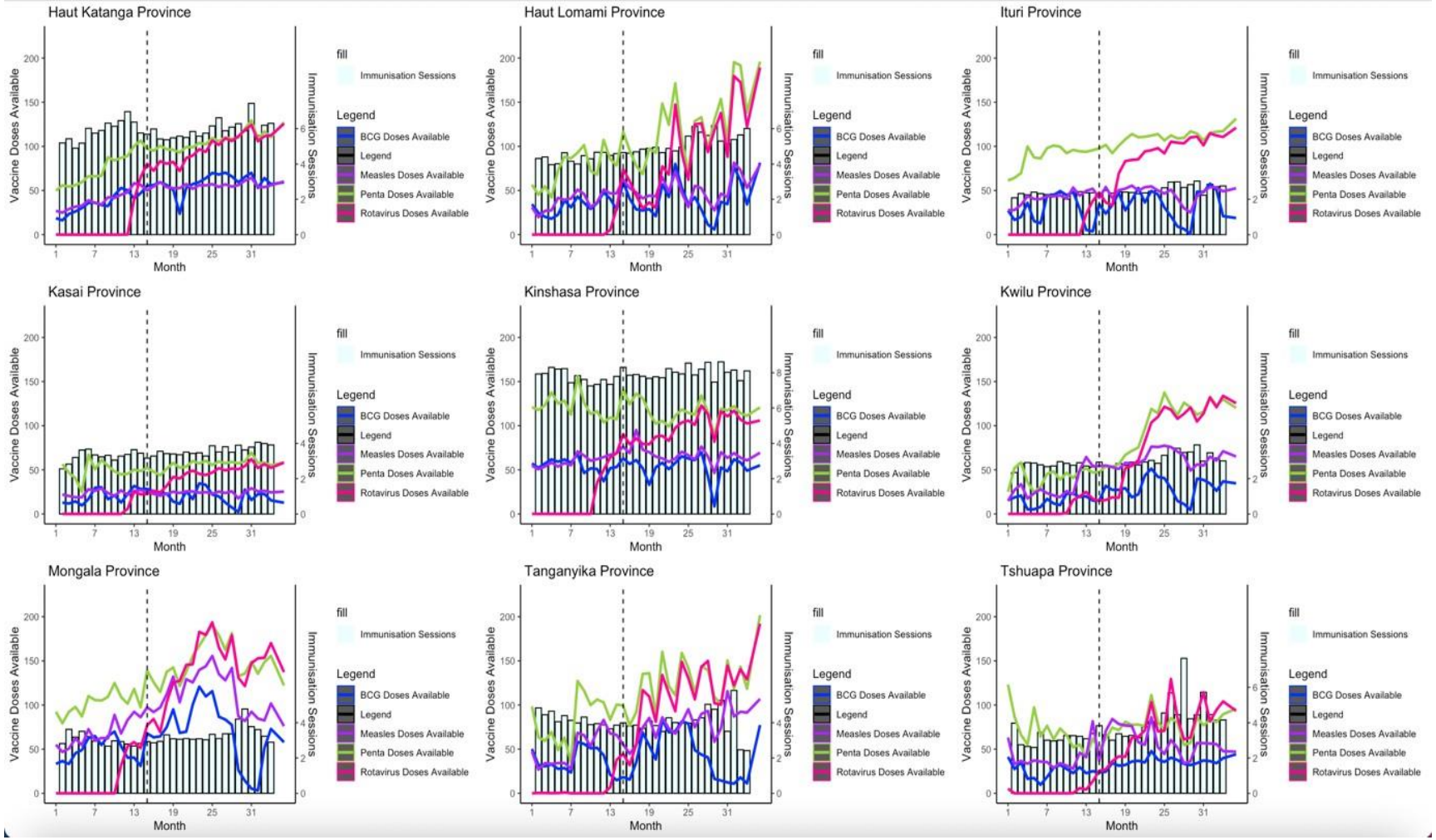
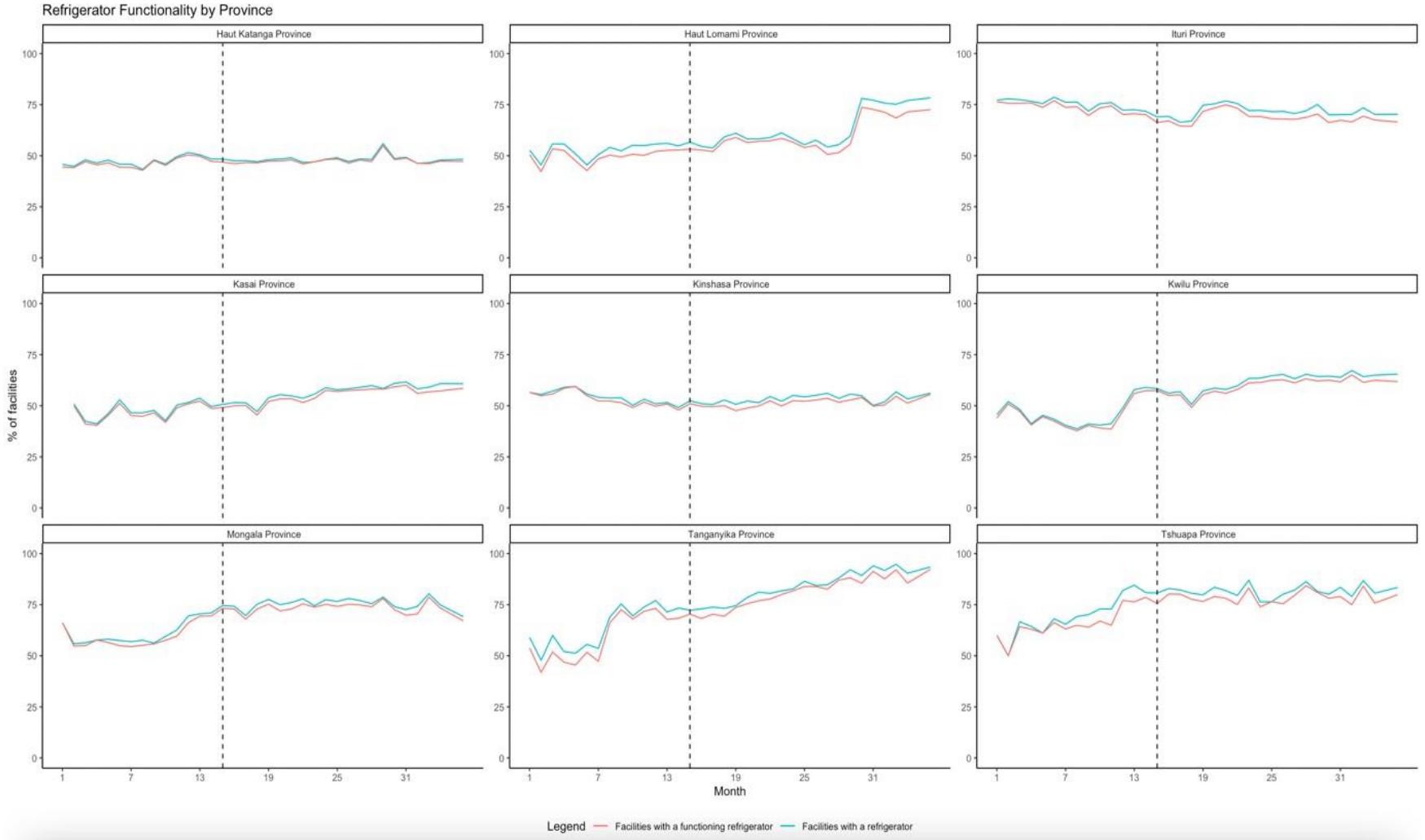


Table 2. Linear Models to test for trend, mean doses over time

Variable	Estimate (Mean Difference)	95% CI
Mean Sessions	0.025	(0.019, 0.030)
% of Facilities with at least 4 sessions per month	0.207	(0.146, 0.269)
Mean BCG Doses	0.376	(0.195, 0.557)
Mean Pentavalent Doses	1.628	(1.399, 1.859)
Mean Measles	0.891	(0.732, 1.050)
Mean Rotavirus	4.531	(4.279, 4.785)

Figure 4. Percentage of Facilities with Refrigerators and Functioning Refrigerators



Supplementary Figures

Figure 1. Mean Immunization Sessions with individual antigen trend lines

Figure 1a. Pentavalent Vaccine Doses Available and Mean Immunization Sessions Held

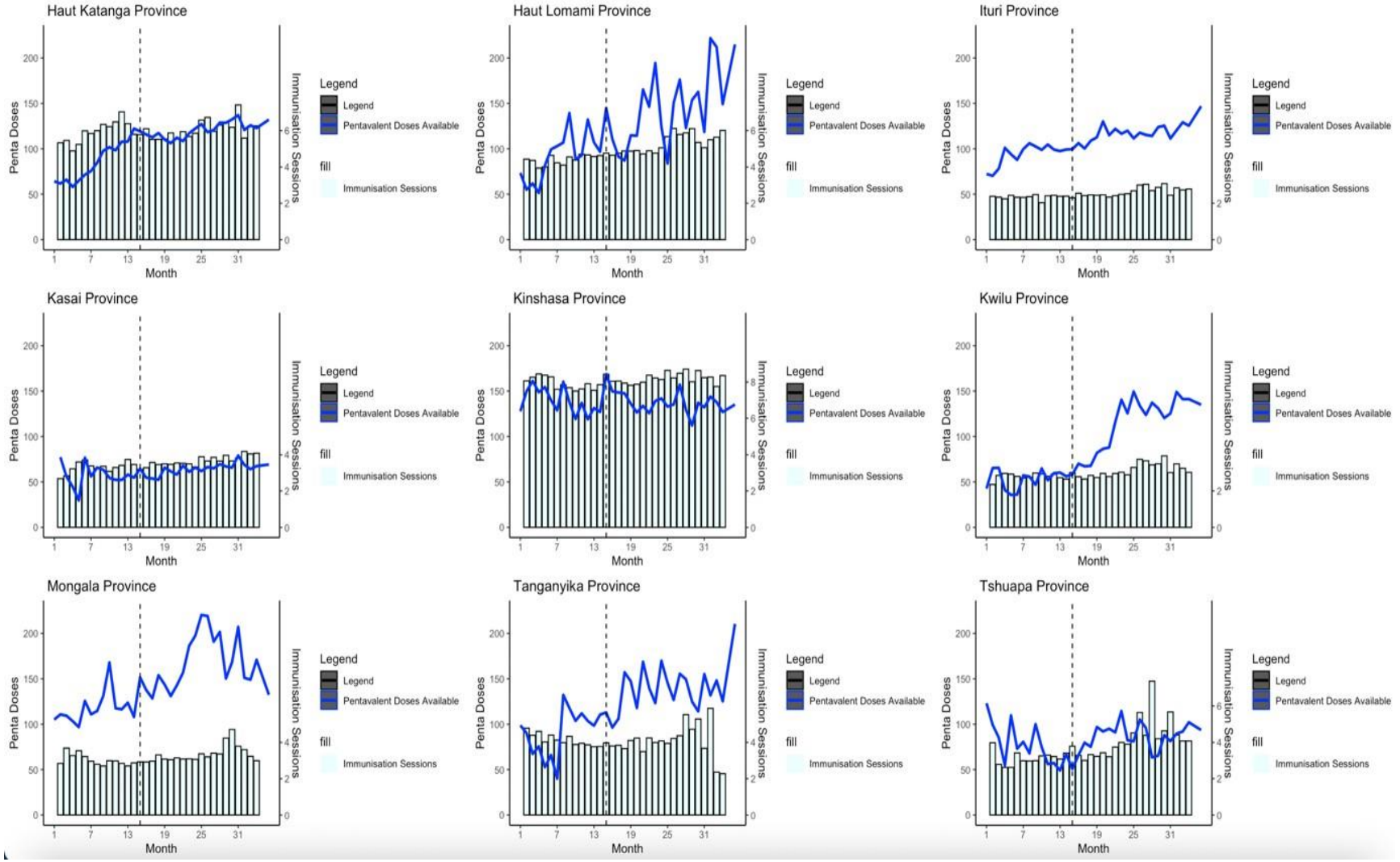


Figure 1b. Measles Vaccine Doses Available and Mean Immunization Sessions Held

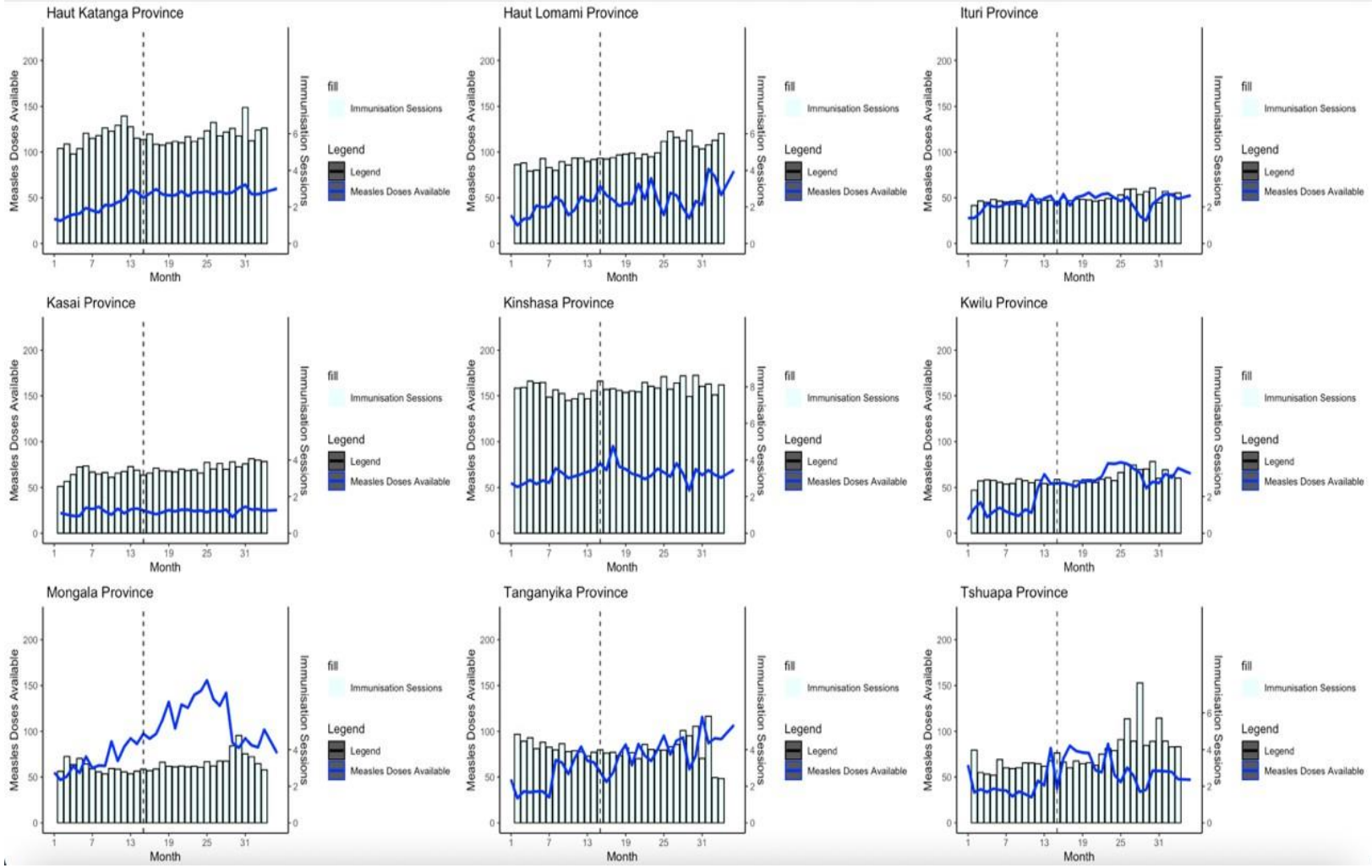


Figure 1c. BCG Vaccine Doses Available and Mean Immunization Sessions Held

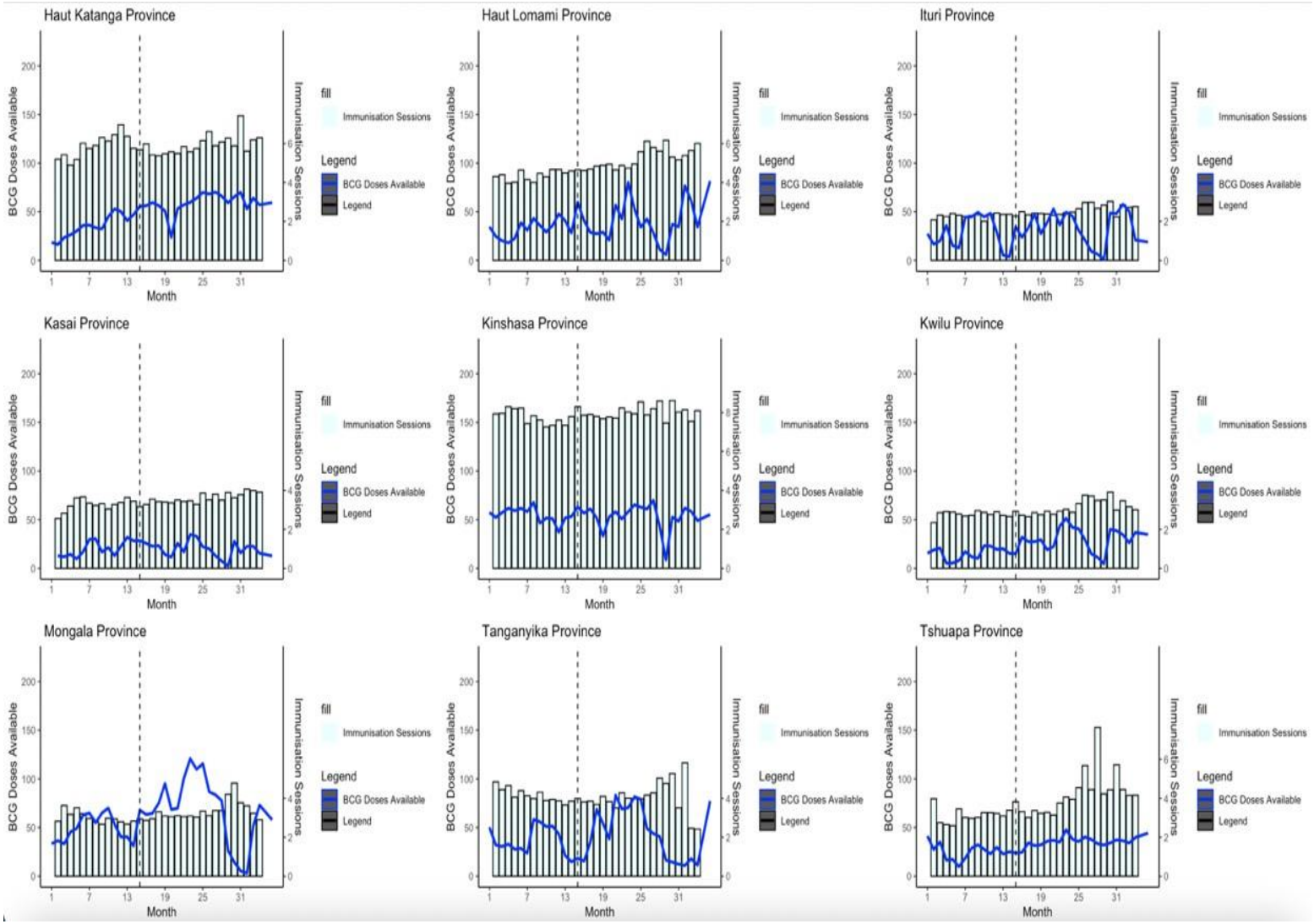


Figure 1d. Rotavirus Vaccine Doses Available and Mean Immunization Sessions Held

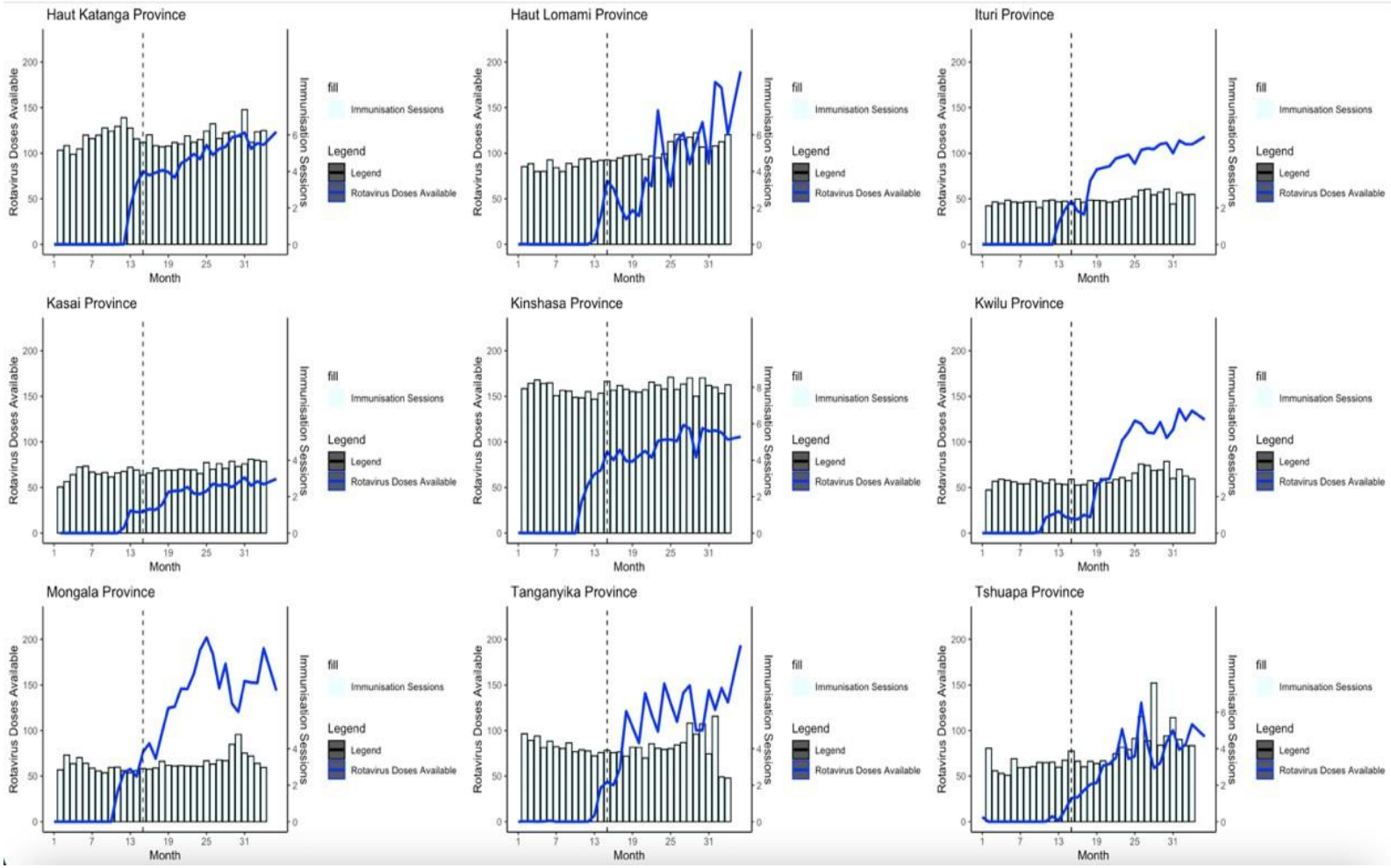
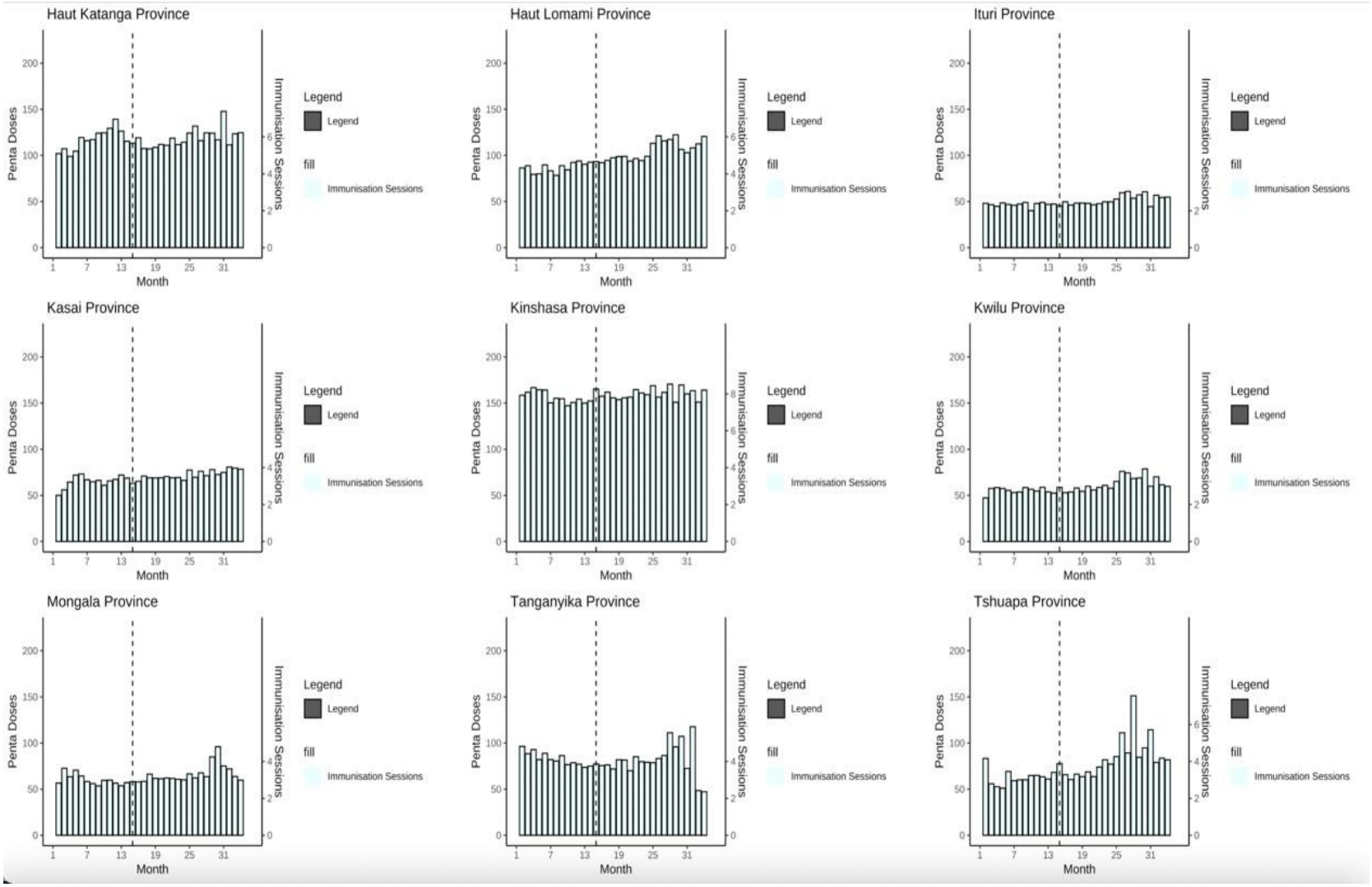


Figure 1e. Mean Immunization Sessions



Chapter 3: The Impact of the Emergency Strategy "Mashako Plan" to Revitalize the Routine Immunization System in DRC: An Interrupted Time Series Analysis

3.1 ABSTRACT

BACKGROUND

Routine immunization (RI) systems have become a global standard for providing consistent access to vaccination services and protecting communities against vaccine-preventable diseases. The Democratic Republic of Congo (DRC) has struggled with low vaccination coverage, with only 35% of children being fully immunized for all antigens in the DRC RI schedule, according to nationally representative surveys. To address this, the DRC national immunization program developed the Mashako Plan, a multipronged policy aimed at revitalizing the RI system by targeting key areas such as vaccine availability, equity in vaccination services, monitoring and evaluation, workforce development, and data quality and management. The objective of this study is to evaluate the impact of the Mashako Plan on RI services in the initial provinces where it was implemented, through an interrupted time series analysis.

METHODS

This study utilizes administrative data at the health facility level from DHIS2 from January 2017 to March 2022. The outcome of interest is the percent change in the number of doses of each vaccine of interest administered per health facility per month from the baseline period to the post-policy implementation period. We conducted an interrupted time series (ITS) analysis with the Mashako Plan implementation in 9 provinces of DRC in October of 2018 as the event of interest.

RESULTS

The analyses show a positive trend in vaccine doses administered for penta3, penta1, and measles vaccines, with an average percent change in doses administered increasing above the background rate of increase for each additional year of the policy. The baseline percentage change over time in doses administered at the time of Mashako implementation were 4.3% for penta3, 3.4% for penta1, and 4.9% for measles vaccine. For each additional year of the policy, there was an increase of 3.8% in the percent change of penta3 doses, 3.8% in the percent change of penta1 doses, and 2.2% in the percent change of measles vaccine doses administered above the background rate of increase.

CONCLUSION

The results of this study support the overall success of the Mashako plan in strengthening the RI system in DRC. These analyses demonstrate the impact of cross-cultural and cross-sectoral collaborations on vaccination services. Additional studies should be conducted to assess the regional impacts of the Mashako Plan in DRC.

3.2 BACKGROUND

Vaccines have been one of the greatest medical achievements in modern history, eradicating smallpox and preventing the spread of many other infectious diseases, which are now considered vaccine preventable diseases (VPDs). Organizations such as the World Health Organization (WHO) and UNICEF estimate that 2 to 3 million deaths are prevented every year through the use of vaccines. Following the success of vaccination campaigns, routine immunization (RI) systems have become the global standard around the world to protect our communities and prevent the spread of infectious diseases. Vaccination campaigns in the form of Supplementary Immunization Activities (SIAs) are extremely expensive and provide short term impact. RI systems are meant to provide consistent access to vaccination services for the most common infectious disease illnesses of childhood in a more affordable, stable and sustainable way.

The Democratic Republic of the Congo (DRC) is the largest country in Central Africa with an estimated population of over 89 million[45]. The 2017-18 MICS survey reported that only 35% of children in DRC were fully immunized for all antigens in the DRC RI schedule[26]. In order to revitalize the RI system, the DRC national immunization program (EPI) worked with partners to develop a policy that would target 5 key areas of immunization services: vaccine availability, vaccination service equity, monitoring and evaluation, workforce development, and data quality and management[23]. This multipronged policy was called the Mashako Plan and aimed to create an emergency mindset around routine immunization that would result in substantial improvements to the system within 18 months of implementation[23]. The Mashako Plan policy was implemented in October of 2018[23].

Due to the size and number of sub-national provinces (26), it was necessary to determine what would be considered the highest priority provinces. The initial plan was to implement the Mashako

Plan in 9 provinces, with roll out to the remaining provinces over a two-year time period. Provinces included in the initial rollout of the Mashako plan were included for several different reasons including population, poor vaccination coverage and political significance. Kinshasa, Ituri, Haut Katanga, Kasai and Kwilu were chosen because of their large populations and Tanganyika, Tshuapa, Haut Lomami and Mongala were chosen because of ongoing VPD outbreaks and low vaccination coverage rates (Figure 1)[23]. These 9 provinces account for 45% of under immunized children in the DRC and include 6,679 of 17,053 health facilities[24].

Despite this policy being implemented and general increases seen in country wide vaccine coverage surveys, minimal specific evaluation has been done to estimate the overall effect of the Mashako Plan policy on the RI system in DRC. A similar study out of Brazil found that administrative data were a reliable source to assess Pneumococcal conjugate vaccine (PCV10) for an ITS analysis[46]. WHO and UNICEF also use administrative data in combination with survey results to evaluate RI systems[47]. While survey data provides an external gold standard for evaluation of immunization services, this paper aims to demonstrate the utility of administrative data in public health/immunization program evaluation analyses. In order to assess the impact of the Mashako Plan policy on RI services in DRC, monthly administrative data from health facilities in the District Health Information System (DHIS2) was used to conduct an interrupted time series (ITS) analysis of the initial 9 provinces where this policy was implemented.

3.3 METHODS

Data Sources

Administrative data at the health facility level from DHIS2 between January 2017 and March 2022. The data were downloaded from DHIS2 at the health facility-month level for all variables of interest[48].

Variables

In the DRC, diphtheria, pertussis, and tetanus vaccines, often referred to as DTP, are administered through the pentavalent vaccine which includes DTP as well as hepatitis B and Haemophilus influenzae type b. The third dose of the pentavalent vaccine (Penta3), which is scheduled to be given at 14 weeks in DRC, was used as the primary outcome variable because it is a standard indicator for the strength and accessibility of a RI system[49].

The first dose of the pentavalent vaccine (Penta1) and the measles vaccine were also evaluated as secondary outcomes. Penta1 is scheduled to be given 6 weeks of age and is commonly used as an indicator of non-vaccination (zero-dose)[50,51]. The first dose of measles vaccine (MCV1) is also often used as an indicator variable for the strength and utilization of the RI system because it is given at 9 months of age and is therefore one of the latest vaccines in the RI schedule.

The outcome of interest is the percent change in the number of doses administered per health facility per month from the baseline period (defined as the year before Mashako Plan implementation) to the post-policy implementation period. The primary outcome of interest is the percent change in the mean number of penta3 doses administered per month per health facility between the baseline period and post-implementation.

The time frame used includes the baseline period from January 2017 until the implementation of the Mashako Plan in October of 2018 (a 2-month lag was included for the rollout of the policy so the actual implementation date in the analyses is December 2018) and the post-implementation period is December 2018 to February of 2022. The event of interest being evaluated is the implementation of the Mashako Plan in December of 2018. Health facilities were included in the

analysis if they were in the 9 provinces where the Mashako Plan was initially rolled out and included at least 30 months of complete data for Penta3, as it was the primary outcome.

Statistical analysis

We conducted an interrupted time series (ITS) analysis with the Mashako Plan implementation in nine provinces of DRC (initial Mashako Provinces) in October of 2018 as the event of interest, visually represented in Figure 2[1]. A dichotomous dummy variable was generated with 0 assigned to pre-implementation and 1 to post-implementation of the policy. A numeric time to policy implementation variable was created for each year before and after implementation. A 2-month lag time was included in the analyses to allow for the scale up of the policy and to see the impact of the Mashako Plan policy, the effective implementation date in the model is therefore December of 2018.

Baseline values were generated for each variable for each health facility. Outlier health facilities months with extreme values for the number of doses administered over 3 standard deviations from the mean were excluded. The percent change was calculated by comparing the doses administered in each month post-implementation to the baseline period before Mashako Plan implementation. The baseline was defined as the average monthly number of doses administered in each facility over the 12-month period prior to implementation of the Mashako Plan. This baseline variable was then used to generate relative change variables.

Assumptions

In order to conduct the ITS analyses, several assumptions need to be made including the assumption that the nine provinces included in this analysis all experience the same 3% population growth rate that the DRC uses nationally to estimate population growth and no significant

migration between provinces that vary by month; we rely on the linear time trend to control for this growth. We also controlled for seasonality with a binary variable for rainy and dry season (dry=May to September) and made the assumption that there are no time-varying uncontrolled confounders that are not included in the model.

Missing data is an issue in DHIS2. In DHIS2 zeros are recorded as NA, the same as missing data points so there is no way to differentiate between true zeros and missing values. In order to understand how much missingness to include in the dataset a series of sensitivity analyses were conducted. With these sensitivity results, the data was restricted to health facilities that included 30 months of data between January 2017 and February 2022.

Ethics

This activity was determined to be exempt from IRB (IRB#22-001553) at UCLA and the data is available from the MoH in DRC upon request.

3.4 RESULTS

Exploratory Analysis (Figure 3, supplemental figure 1)

The scatterplots provided show the general trends of both the raw numbers of penta3, penta1 and measles doses administered over time from 2017 (year=-2) to 2022 (year=3) as well as the calculated percentage change outcome calculated between the baseline (year=-1) year and each subsequent time point, trend over time. These plots generally show a positive trend indicating an increase in vaccine doses administered over time.

Interrupted Time Series Analysis (Figure 4)

At the time of the implementation of the Mashako Plan (Time = 0) the average percent change in penta3 doses per facility between baseline and implementation was 4.3% (the background rate of change). For each additional year of the policy, there was an additional 3.8% positive percent change in penta3 doses administered above the background rate of increased vaccination. At the time of the Mashako Plan implementation (Time = 0) for penta1 and measles vaccine, the average percent change in doses per facility between baseline and implementation (background rate of change) were 3.4%, and 4.9% respectively. With each additional year of the policy, there was a positive percent change in penta1 doses administered above the background rate of increased vaccination, which was 3.8%. Similarly, for measles vaccine doses, there was an additional 2.2% percent change above the background rate of increased vaccination. These figures are summarized in Table 1.

The plots in Figure 4 demonstrate an increasing trend in the percentage change in doses administered for all vaccines of interest over time. The magnitude of the change increased from year to year, which suggests that the trend of the percentage change in vaccine doses administered between 2018 and each subsequent year is increasing over time. The mean difference in percent change between the number of penta3 doses administered in the baseline year and the first year of Mashako Plan implementation is 1.078. In the second year the mean difference is 1.141. In the third year the mean difference is 1.204 and in the fourth year it is 1.267 (supplementary Table 1). We see similar trends in the percent change in both penta1 and measles doses administered. The plots in Figure 4 also include the counterfactual values for the expected percentage change over time if the Mashako Plan were not implemented.

The analyses assume that the national ~3% population growth per year is consistent across provinces and that provinces are relatively homogenous. In order to validate this assumption, we conducted the same interrupted time series analysis for each province to review the estimates between provinces (supplementary table 2). Based on the results, we found that the estimated change in percentage change in doses of vaccines administered associated with the implementation of Mashako Plan, varied across provinces.

In Kinshasa, the interaction term, which shows the change following the intervention, of 0.166 indicates a significant positive relationship between Mashako implementation and percentage change in doses of vaccines administered over time. The effect size was 0.299, suggesting that, on average, there was a 0.299 percentage point increase in the change in penta3 vaccine doses administered associated with the implementation of the Mashako Plan in Kinshasa.

In Mongala, the interaction term is significant and negative (-0.046), indicating a weaker relationship between Mashako implementation and percentage change in Penta3 vaccine doses administered over time. However, the effect size was still positive (0.159), suggesting a 0.159 percentage point increase in the change in penta3 vaccine doses administered over time with the Mashako Plan implementation in Mongala. The negative interaction term indicates that the relationship between Mashako Plan implementation and the percentage change in vaccine doses administered over time is weaker in Mongala than other provinces, but the positive effect size suggests that there is still an increase in the percentage change in penta3 doses administered after the implementation of the Mashako Plan overall.

For penta1, there was a significant positive interaction term for Haut Katanga (0.013) and Kinshasa (0.162), indicating an increase in the percentage change in doses of vaccine administered over time

in these provinces. However, for Kwilu (-0.057) and Mongala (-0.028), there was a significant negative interaction term, suggesting a decrease in the percentage change in doses of vaccine administered over time in these provinces.

For measles, there was a significant positive interaction term for Haut Katanga (-0.008) and Kinshasa (0.055), indicating an increase in the percentage change in doses of vaccine administered over time in these provinces. However, for Kwilu (-0.077), there was a significant negative interaction term, suggesting a decrease in the percentage change in doses of vaccine administered over time in this province.

These results suggest that while there was an overall positive percentage change in doses of vaccine administered over time, the results varied across provinces and across vaccines. In some provinces, such as Haut Katanga and Kinshasa, there was a significant increase in the percentage change in doses of vaccine administered over time for all three vaccines. In other provinces, such as Kwilu and Mongala, there was a decrease in the percentage change in doses of vaccine administered over time for penta1 and penta3.

Sensitivity Analysis

In order to evaluate if the 9 Mashako Plan provinces are similar enough to be evaluated together we conducted additional sensitivity analyses in which we conducted the ITS analyses at the provincial level and found that in the 9 initial provinces, they generally have small estimates, with two of the 9 showing a small negative impact.

First the ITS analysis was run multiple times requiring different numbers of months of available data ranging from 5 to 40 months, in increments of 5. These analyses showed that as the allowable

amount of missing data was reduced, the estimate of the ITS model goes down (see Supplementary Figure 1). However, given the issue of missing data, we also conducted the same sensitivity analyses but replaced all missing values with zeros. This resulted in an opposite trend with the estimates increasing along with the number of months of data required (see Supplementary Figure 2). Due to the results of this analyses, facilities with 30 months or more of complete data, over the course of the 63 months, were included the analyses.

3.5 DISCUSSION

Our study found a significant positive percentage change in the number of doses of penta3 vaccine administered after the implementation of the Mashako Plan to revitalize the routine immunization system in the DRC. The average percent change in penta3 doses administered before the plan was 4.3%, considered the background rate of change. After the plan, there was an additional positive percent change of 3.8% per year in penta3 doses administered above the background rate of increased vaccination for each additional year of the policy. These yearly results provide a strong picture of the trend of penta3 vaccine doses administered. The initial phase of the Mashako Plan was designed to improve access (as opposed to generate demand) for immunization services[23]. Penta3 was evaluated as the primary outcome of interest because it is a standard indicator for the functionality and accessibility of RI systems and a better proxy for full immunization since it accounts for drop-out that occurs after the first dose[49].

The study also explored penta1 and measles vaccine doses as secondary outcomes of interest, in addition to penta3, to see how the estimates differ between these commonly used indicator vaccines and to explore if there is a difference in the estimates. Penta1 is used to measure zero-dose estimtes[20] and measles is a commonly used indicator vaccine for utilization of the RI system[51].

However, there was a large measles outbreak in DRC in 2019, and there are often large SIAs for measles, which may cause measles vaccination rates to be an overestimate of the strength of the routine immunization system[52,53]. In these analyses, it was found that the results were fairly similar for penta3 and penta1 but dropped slightly for measles. This may be because measles is given later in the vaccine system or because there are common measles campaigns in which vaccinations may not be entered into the routine system record. Overall, the results suggest that the Mashako Plan was successful in improving access to and uptake of routine immunization services in the DRC.

The Mashako plan includes a unique set of revitalization strategies that focused on the accessibility side of the RI system influencing cold chain functionality to vaccine availability, personnel support and finances. This evaluation attempts to assess the true impact of these policy activities beyond the baseline improvements happening before the implementation of this plan.

While there are currently limited publications in the literature about this emergency strategy to revitalize a RI system in DRC, the Mashako Plan, similar revitalization strategies have been implemented in other countries and found similar success. In India, a similar cross-sectoral strategy was implemented to improve immunization services called "Mission Indradhanush" and found that the intensified strategy with cross-sectional participation and intense monitoring improved vaccination rates[54]. Other publications have also used administrative data from health information systems such as DHIS2 to conduct interrupted time series analyses, such as the article my Ahmed et al. that evaluated the impact of the COVID-19 pandemic on health care utilization in 18 LMICs using an interrupted time series analysis of administrative data[55]. This study found that healthcare utilization in DRC decreased by ~10% due to the COVID-19 pandemic although this estimate varies widely by location and several other factors[55]. Another study that used an ITS analysis on

administrative data to assess the impact of COVID-19 on maternal and child health service utilization in eight sub-Saharan African countries found minimal impacts in DRC[56]. This study adjusted for seasonality as we did in our analyses.

The Mashako Plan in DRC consists of a series of policy strategies and actions at national, provincial and local levels to revitalize the routine immunization system. These strategies include activities to strengthen coordination, service delivery, vaccine availability, real-time monitoring and evaluation[23]. Since the implementation of this program in the initial 9 provinces in 2018 there has been an overall increase in vaccination rates in these provinces of DRC. In these analyses we assume that there is no significant movement between provinces, however due to active conflict in Eastern DRC, additional research should look into the migratory patterns between provinces. According to the Ministry of Health there are 53 health zones that are considered insecure and 58 health zones that are considered difficult to access, while we know that these numbers must vary throughout the year, particularly for accessibility, the data available is all static and therefore inappropriate for use in these types of analyses. In the future more precise estimates for monthly changes in access and security would be helpful information for these analyses. Some accessibility is caused by changes in seasonality, which is adjusted for in these analyses. However, the only seasonality information available was a simple binary dry and rainy season which does not take into consideration seasonal variability between provinces. The COVID-19 pandemic was not adjusted for in these analyses, results of the evaluation of EPI mobile supervision data and other studies such as the Hategeka et al. study that looked at the impact of COVID-19 in DRC did not see significant impacts on the RI system[34,39,56]. However, a study in Cameroon found that when using DHIS2 data to evaluate the impact of COVID-19 on RI services, the long-term impact was masked, therefore additional studies should look at this issue with different data sources in DRC[57].

The analyses also assumes that the national ~3% population growth per year is consistent across provinces. In order to validate this assumption, we conducted the same interrupted time series analysis for each province individually in order to review the ITS estimates between provinces (results in supplementary table 2). This sensitivity analysis shows that there is variation in the impact of the Mashako Plan between provinces, therefore a more in-depth analysis by province would be ideal. A sensitivity analysis was also conducted to determine the impact of including different levels of complete data in the analyses. Outlier health facilities months with extreme values for the number of doses administered over 3 standard deviations from the mean were excluded, however some studies suggest that using the Median Absolute Deviation (MAD) estimates may produce more accurate estimates, future analyses should look at this as a sensitivity analysis to determine which method to use when identifying health facility months to include[58]. ITS analyses are subject to challenges of common shock, two limitations in these analyses were the inability to access the data for monthly stock out of vaccinations and the healthcare worker strikes that occurred in several provinces in 2021.

There are inherent challenges that come with using data collected in the DHIS2 system. One of the significant challenges relates to missing data, therefore sensitivity analyses were conducted to understand the impact of potential zeros on our estimates. When all missing values were replaced with zeros, we saw an upward trend in the estimates. Therefore, it is possible that our results underestimate the effects given the fact that NA values were all treated as missing in our analyses.

3.6 CONCLUSION

The results of these analyses help to support the large amount of government and donor resources that went into the development of the Mashako Plan. This policy was a key factor in the agenda of

the new government, President Tshisekedi highlighted universal healthcare and childhood immunizations as a priority for the country. This political support helped set the stage for the initial roll out of the Mashako Plan and facilitated collaboration across countries and sectors. These analyses aim to show the impact that these cross-cultural and cross-sectoral collaborations can have on vaccination services. While these results vary across provinces, they give an overall view of the success of this program in the 9 provinces that initially implemented the strategy and give confidence and support to the rollout of the next phase of the plan, Mashako 2.0[59]. Mashako 2.0 will add additional indicators for monitoring and evaluation to the existing system[59]. These results demonstrate the utility of administrative data to evaluate program impact when survey and other time-series data are limited. They also suggest that this strategy to revitalize the RI system can rapidly and successfully improve, at least in the short term, the vaccine administration. However, additional analyses are needed to evaluate regional differences in more detail as well as the impact of the strategy on different indicators such as cold chain.

Tables and Figures

Figure 1. Map Mashako Province Rollout

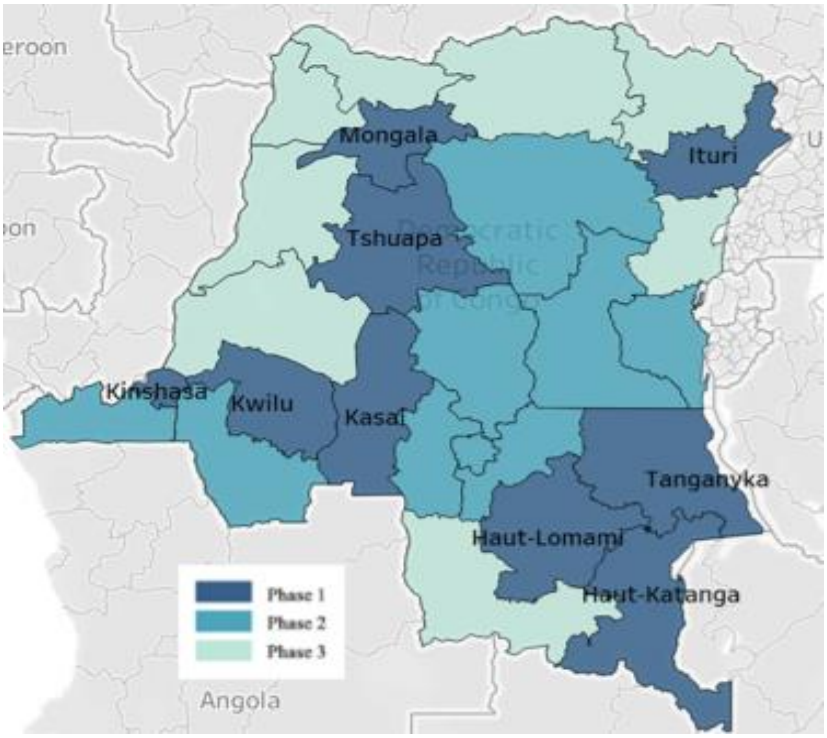
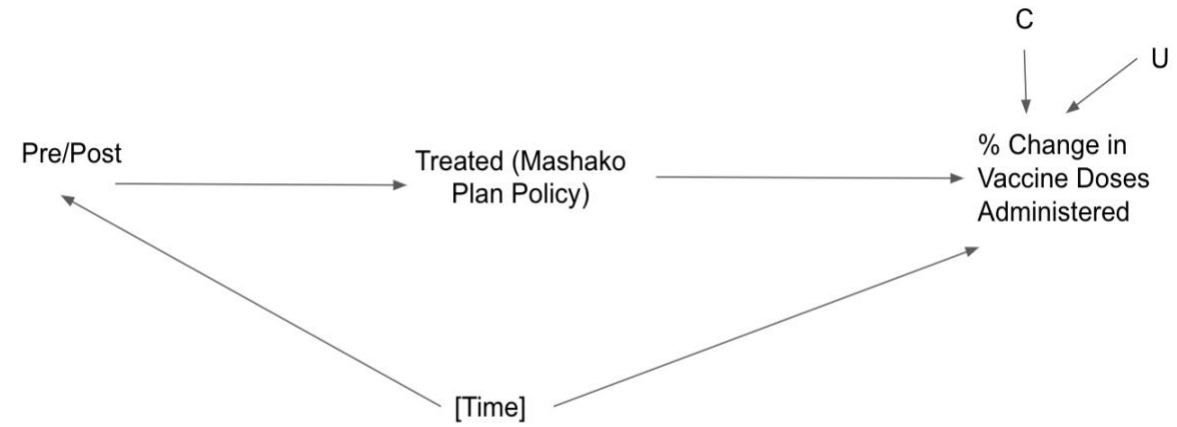


Figure 2: DAG of Interrupted Time Series Analysis of the Impact of Plan Mashako on percent change in vaccine coverage (penta3, penta1, measles)



Time= month (Jan 2017- Present)
Pre/Post= dummy variable for pre-post intervention
C= time-varying covariates (season)
U= unmeasured covariates

E(Y|time,post,c)= $\beta_0 + \beta_{Time} time + \beta_{Pre/Post} pre/post + \beta_{Time*Pre/Post} time * pre/post + \beta_C c$

Time= time elapsed since the start of the study (months starting with January 2017)

Pre/Post= dummy variable for pre-intervention (Post=0) and post-intervention (Post=1)

C=potential time-varying covariates (seasonality)

$\beta_{Pre/Post}$= effect of interest (level change following implementation of the Mashako plan)

Figure 3. Scatterplots of outcomes of interest: a. Penta3 Percent Change in doses administered from baseline year (year before Mashako implementation) to each subsequent year, b. Penta1 Percent Change in doses administered from baseline year (year before Mashako implementation) to each subsequent year, c. Measles Percent Change in doses administered from baseline year (year before Mashako implementation) to each subsequent year.

Figure 3a

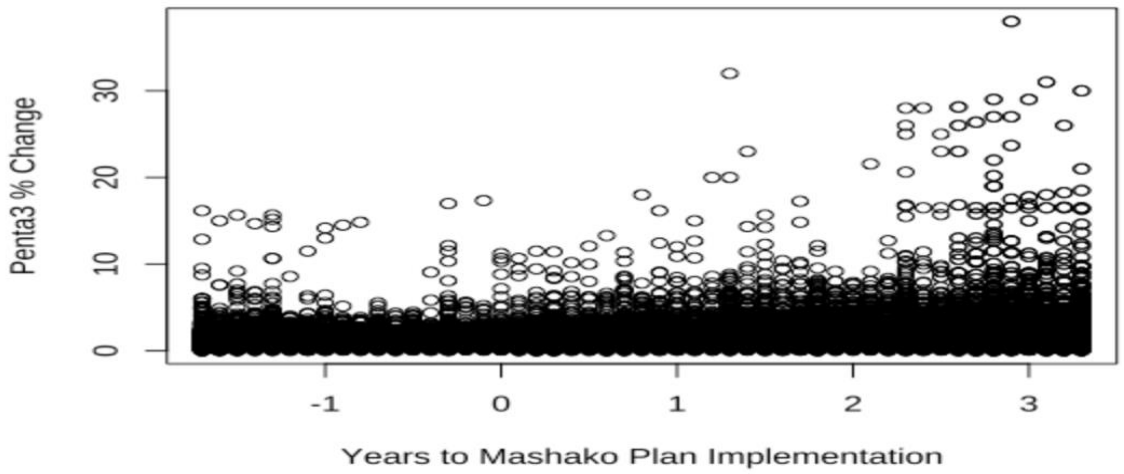


Figure 3b

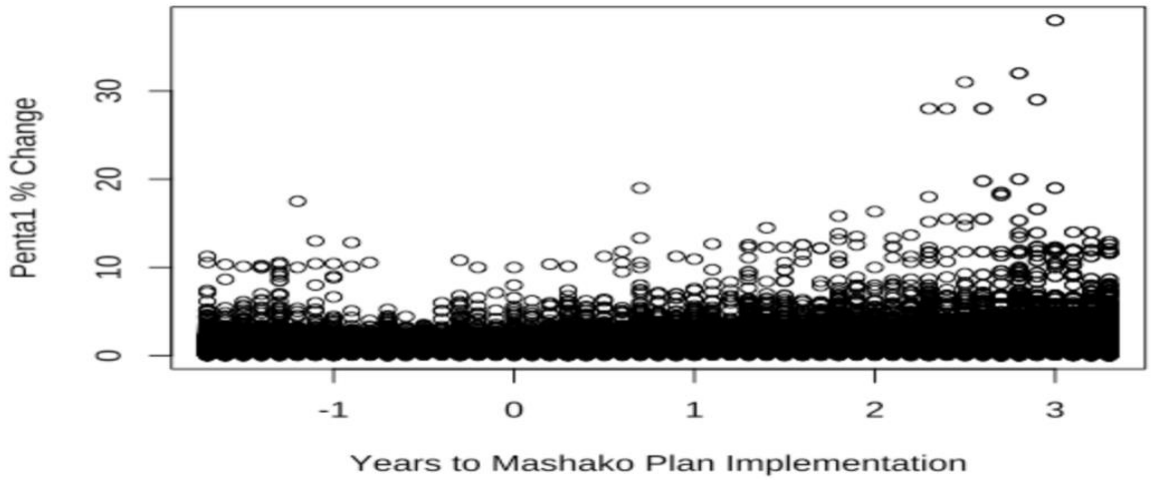


Figure 3c

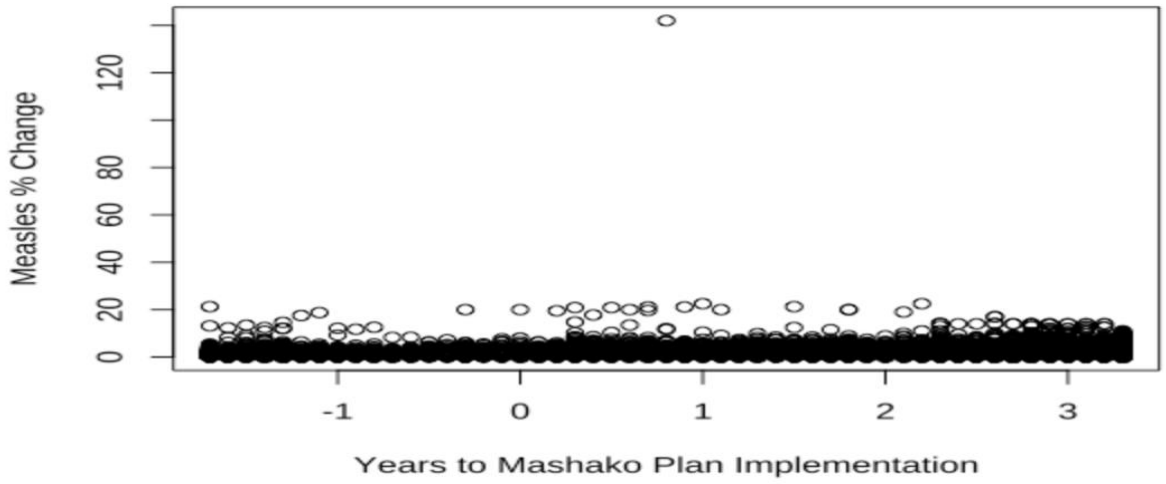

Measles % Change
0
20
40
60
80
120
-1
0
1
2
3
Years to Mashako Plan Implementation

Figure 4. ITS Estimates by Year Overall: a. Plot of percent change in the percent of Penta3 doses administered, comparing baseline (2018) to each subsequent year, b. Plot of percent change in the percent of Penta1 doses administered, comparing baseline (2018) to each subsequent year, c. Plot of percent change in the percent of Measles doses administered, comparing baseline (2018) to each subsequent year

Figure 4a

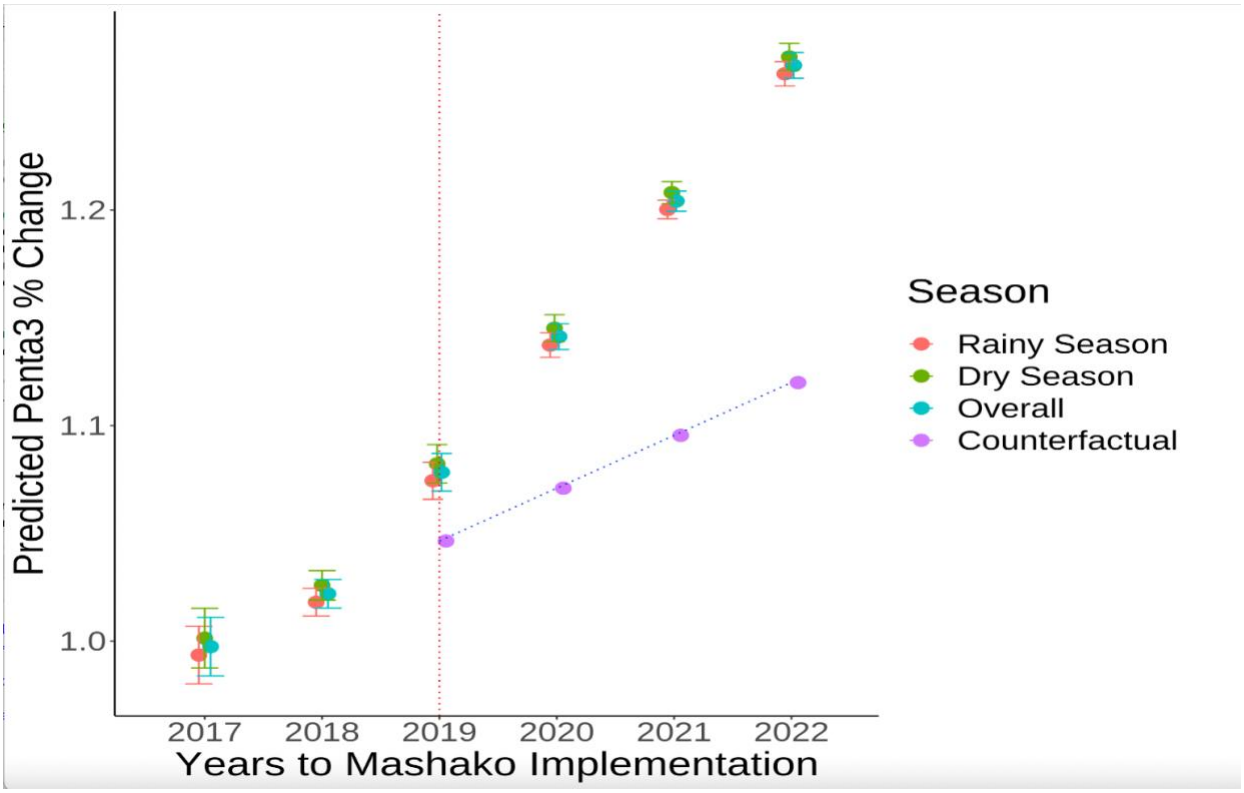


Figure 4b

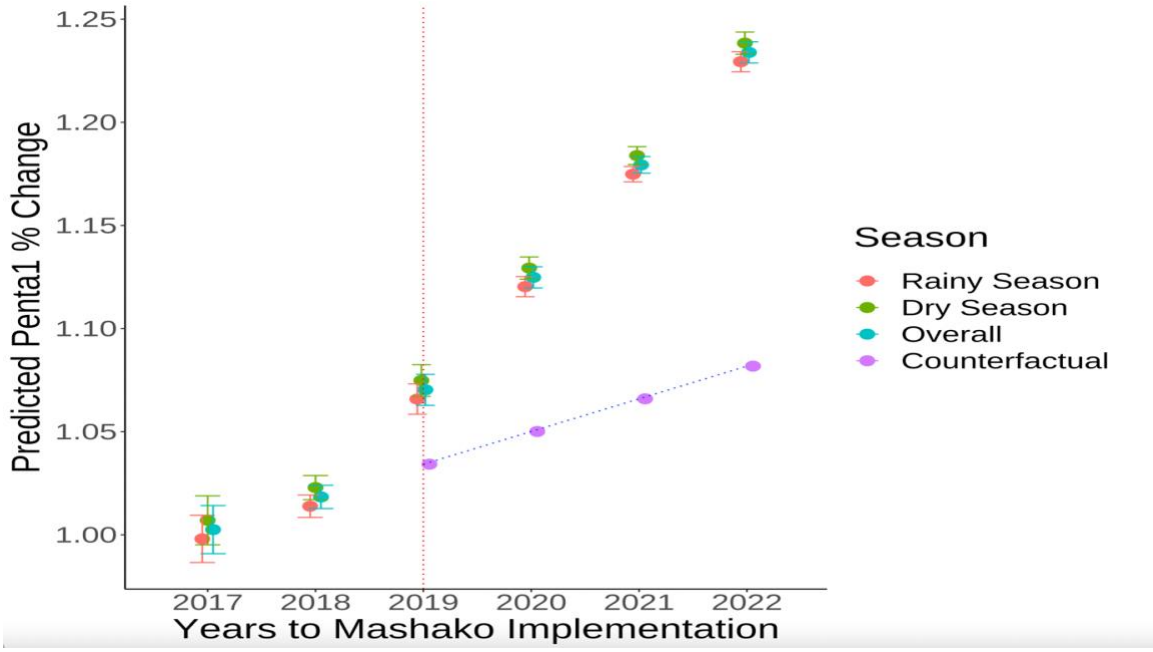


Figure 4c

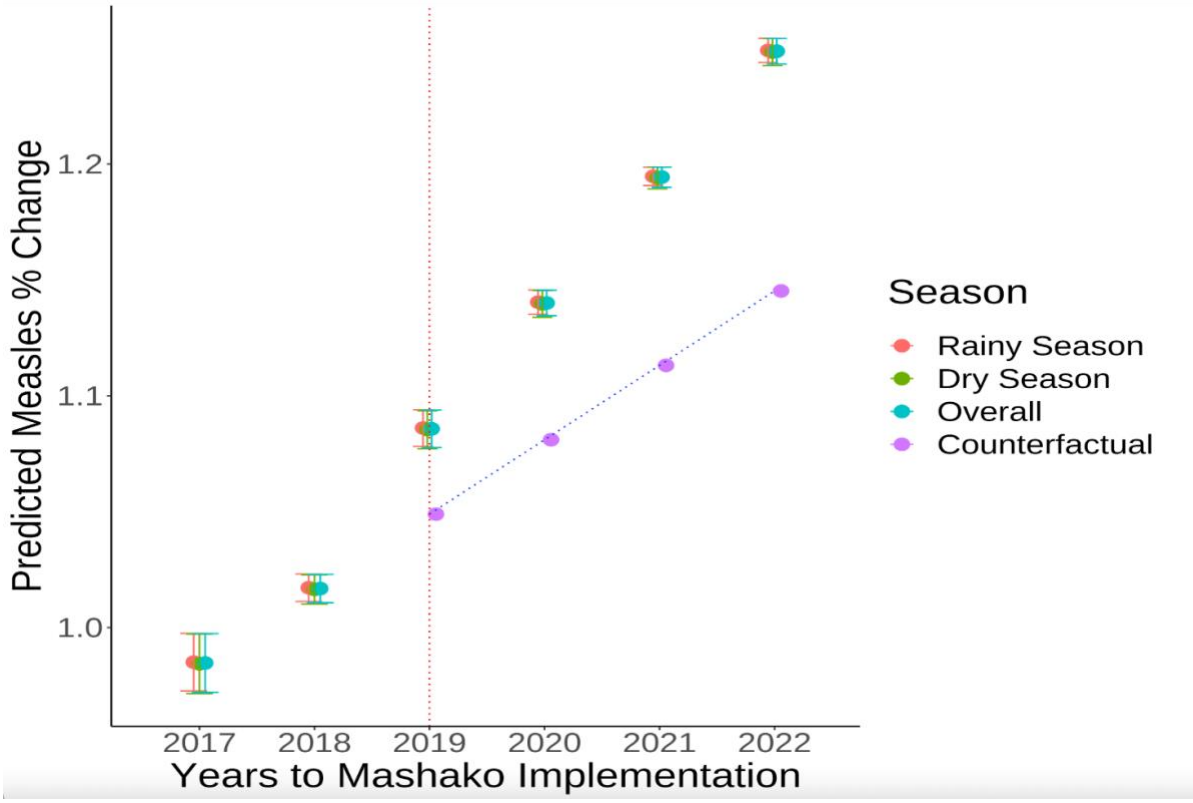


Table 1. Estimates from ITS Analysis by Antigen

	Penta3			**Penta1**			**Measles**		
	Mean Difference	Std. Error	95% CI	Mean Difference	Std. Error	95% CI	Mean Difference	Std. Error	95% CI
Mashako*Time Interaction	0.038	0.005	(0.028, 0.049)	0.038	0.005	(0.029, 0.047)	0.022	0.005	(0.012, 0.032)

Supplementary Tables/Figures

Figure 1. Cutpoints evaluating HF to include with varying amounts of missing data- decided to include facilities with at least 30 months of data

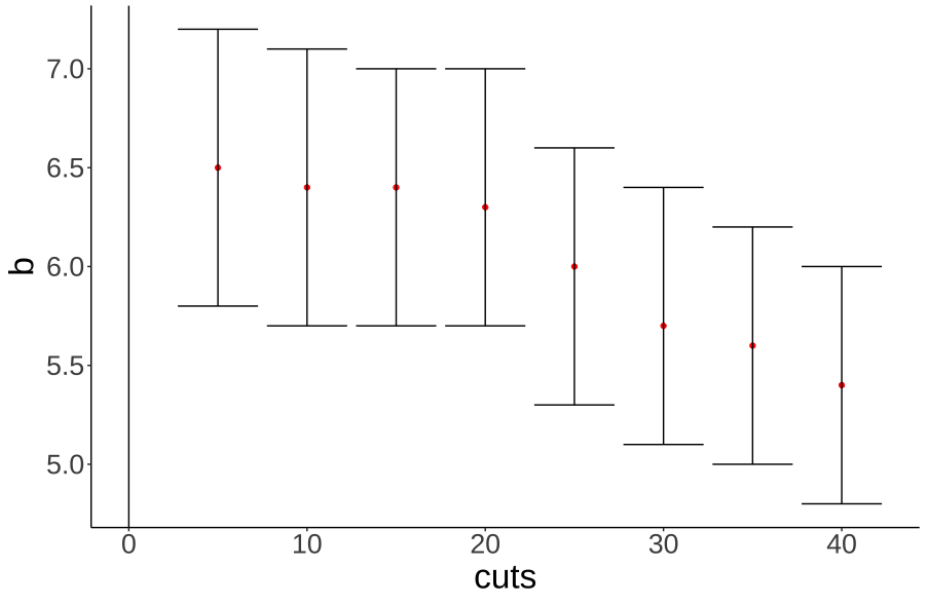


Figure 2. Cutpoints evaluating HF to include with varying amounts of missing data when replacing all NA values with 0

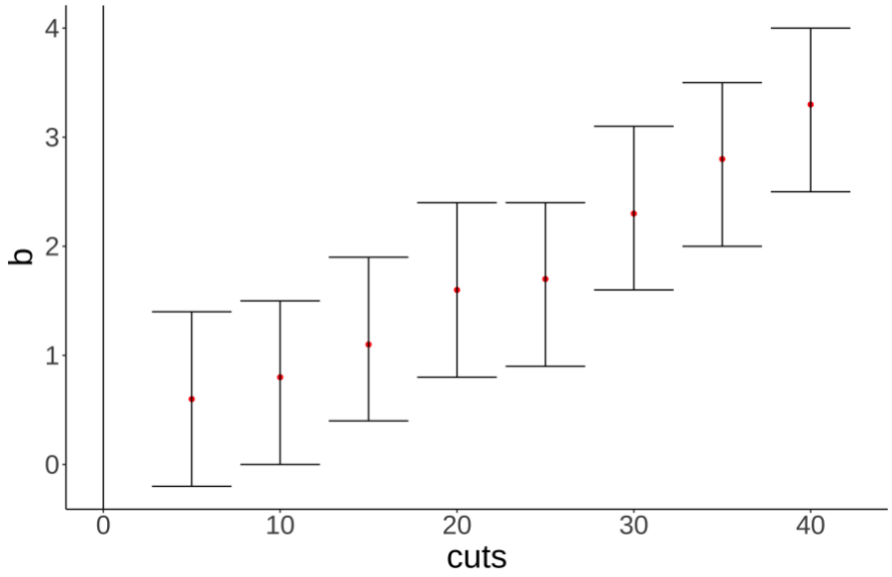


Figure 3. Scatterplots of outcomes of interest: a. Penta3 doses administered from baseline year over time b. Penta1 doses administered from baseline year over time, c. Measles doses administered from baseline year over time.

Figure 3a. Penta3 Vaccine Doses Administered

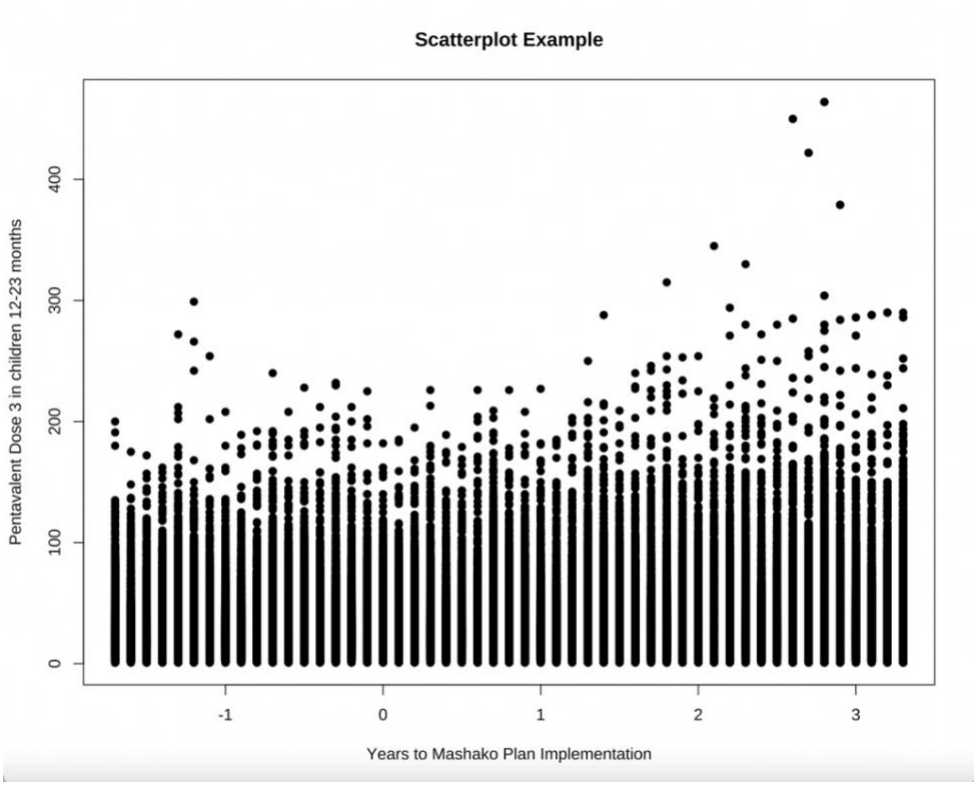


Figure 3b. Penta1 Vaccine Doses Administered

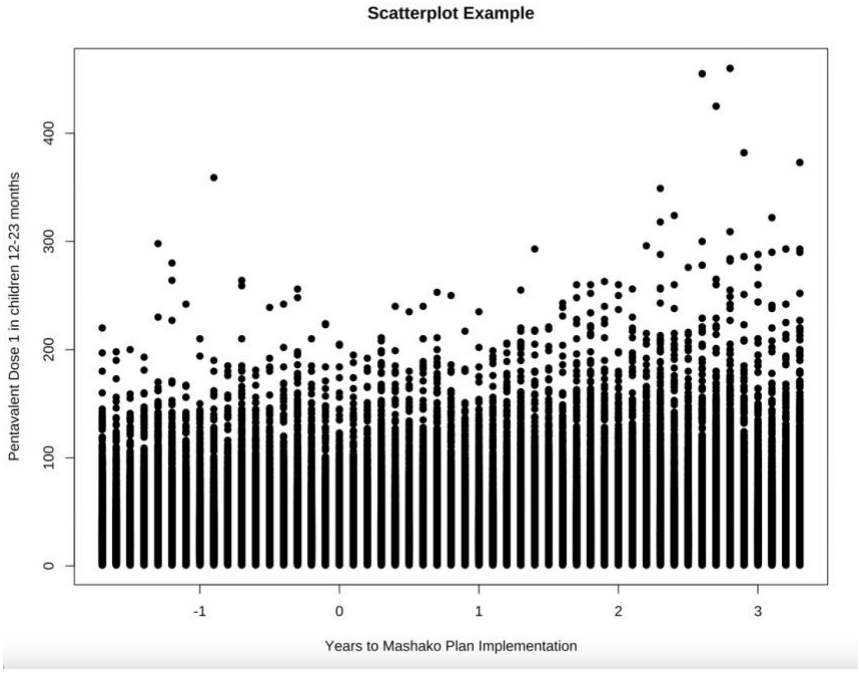


Figure 3c. Measles Vaccine Doses Administered

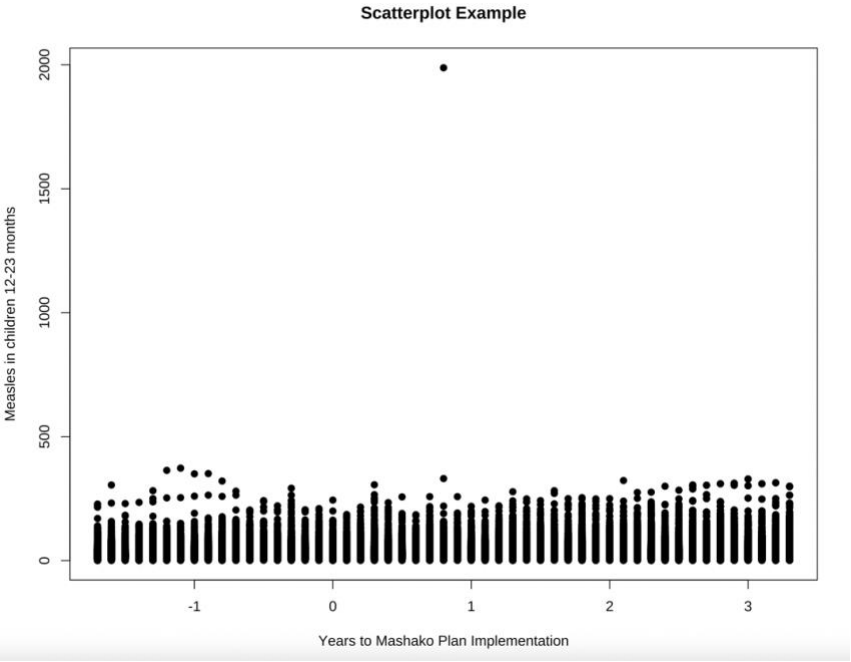


Table 1. Yearly estimates Tables

Table 1a. Yearly estimates for Penta3

Penta3	Rainy		Dry		Overall	
Years to Mashako	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
-2	0.994	(0.980, 1.007)	1.001	(0.988, 1.015)	0.997	(0.983, 1.011)
-1	1.018 (REF)	(1.012, 1.024)	1.025 (REF)	(1.019, 1.033)	1.022 (REF)	(1.015, 1.029)
0	1.074	(1.066, 1.083)	1.082	(1.073, 1.091)	1.078	(1.069, 1.087)
1	1.137	(1.132, 1.143)	1.145	(1.139, 1.151)	1.141	(1.135, 1.147)
2	1.200	(1.196, 1.205)	1.208	(1.202, 1.213)	1.204	(1.199, 1.209)
3	1.263	(1.258, 1.269)	1.271	(1.264, 1.277)	1.267	(1.261, 1.273)

*In code -2=2017, -1=2018, 0=2019, 1=2020, 2=2021, 3=2022

Table 1b. Yearly estimates for Penta1

Penta1	Rainy		Dry		Overall	
Years to Mashako	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
-2	0.998	(0.987, 1.009)	1.007	(0.995, 1.019)	1.003	(0.991, 1.014)
-1	1.014 (REF)	(1.008, 1.019)	1.023 (REF)	(1.017, 1.029)	1.018 (REF)	(1.013, 1.024)
0	1.066	(1.058, 1.073)	1.075	(1.067, 1.082)	1.070	(1.063, 1.078)
1	1.120	(1.115, 1.125)	1.129	(1.124, 1.135)	1.124	(1.120, 1.130)
2	1.175	(1.171, 1.179)	1.184	(1.180, 1.188)	1.179	(1.175, 1.183)
3	1.229	(1.225, 1.234)	1.238	(1.233, 1.243)	1.234	(1.229, 1.239)

Table 1c. Yearly estimates for Measles Vaccine

Measles	Rainy		Dry		Overall	
Years to Mashako	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
-2	0.985	(0.973, 0.998)	0.984	(0.972, 0.997)	0.985	(0.972, 0.997)
-1	1.017 (REF)	(1.011, 1.023)	1.016 (REF)	(1.010, 1.023)	1.017 (REF)	(1.011, 1.023)
0	1.086	(1.078, 1.094)	1.085	(1.077, 1.094)	1.086	(1.078, 1.094)
1	1.140	(1.135, 1.146)	1.140	(1.134, 1.146)	1.140	(1.135, 1.146)
2	1.195	(1.191, 1.199)	1.194	(1.189, 1.199)	1.194	(1.190, 1.199)
3	1.249	(1.244, 1.254)	1.248	(1.243, 1.254)	1.249	(1.243, 1.254)

Table 2. Table with ITS outcomes by province (Initial 9 provinces only)

	Penta3			Penta1			Measles		
Province	Mashako* Time Interaction	95% CI	Effect size	Mashako* Time Interaction	95% CI	Effect size	Mashako* Time Interaction	95% CI	Effect size
Haut Katanga	0.019	(-0.008, 0.050)	0.299	0.013	(-0.011, 0.037)	0.243	-0.008	(-0.069, 0.053)	0.309
Kasai	0.009	(-0.012, 0.029)	0.157	-0.005	(-0.026, 0.015)	0.138	0.004	(-0.014, 0.022)	0.139
Kinshasa	0.166	(0.110, 0.234)	0.316	0.162	(0.112, 0.213)	0.277	0.055	(-0.052, 0.163)	0.275
Kwilu	-0.037	(-0.054, -0.021)	0.078	-0.057	(-0.075, -0.040)	0.041	-0.077	(-0.098, -0.057)	0.049
Mongala	-0.046	(-0.059, -0.032)	0.159	-0.028	(-0.042, -0.014)	0.146	-0.059	(-0.074, -0.043)	0.164
Tanganyika	0.030	(-0.008, 0.057)	0.084	0.046	(0.019, 0.073)	0.083	0.024	(-0.021, 0.070)	0.180
Tshuapa	0.017	(0.004, 0.029)	0.083	0.019	(0.007, 0.032)	0.068	-0.009	(-0.024, 0.006)	0.085
Haut Lomami	0.065	(0.048, 0.080)	0.076	0.099	(0.054, 0.145)	0.078	0.061	(0.039, 0.083)	0.116
Ituri	0.056	(0.042, 0.069)	0.133	0.059	(0.045, 0.074)	0.131	0.092	(0.072, 0.112)	0.140

Chapter 4: Rotavirus vaccine introduction in the DRC: a comparative interrupted time series analysis

4.1 ABSTRACT

BACKGROUND

The Democratic Republic of the Congo (DRC) has a high burden of diarrheal disease, with more than 22,000 children under 5 dying from the disease in 2018 alone. Rotavirus is a major contributor to this burden, causing 40-60% of diarrheal disease cases in children under 5 in the DRC. This analysis focuses on the impact of the new rotavirus vaccine, ROTASIIL, in provinces that were part of the Routine Immunization revitalization plan, Mashako Plan, which aims to strengthen the routine immunization system in the country, compared to the introduction in provinces without this revitalization strategy.

METHODS

Data was sourced from the District Health Information Software 2 (DHIS2), and the primary outcome of interest was cases of simple diarrhea with dehydrated and severe dehydrated diarrhea also evaluated. Between January 2018 and December 2020, 8,536 health areas reported 6,926,447 cases of simple diarrhea, 1,321,194 cases of dehydrated diarrhea, and 311,979 cases of severe diarrhea. Over the time period of January 2020 to December 2020, after the rotavirus vaccine was introduced, 2,907,812 initial doses of the rotavirus vaccine were administered in those same health areas. The study used a series of Comparative Interrupted Time Series (CITS) analyses to compare the change in diarrheal disease cases between provinces that had implemented the Mashako Plan and those that had not.

RESULTS

The results of the analysis suggest a small and generally non-significant effect of the rotavirus vaccine on the incidence rates of diarrhea for the Mashako group, with the precise effect varying depending on the severity of diarrhea, with an IRR of 0.984 for simple diarrhea cases, an IRR of 1.001 for dehydrated diarrhea cases and an IRR of 0.998 for severely dehydrated diarrheal cases in non-Mashako provinces. In Mashako provinces the IRRs do not vary significantly with IRRs of 0.999, 1.005, and 0.995 for simple, dehydrated and severely dehydrated diarrheal cases respectively. ITS analyses that look at all provinces together, adjusting for month of the Mashako plan implementation also found minimal impact with IRRs of 0.989, 0.991 and 0.993 for simple, dehydrated and severely dehydrated diarrheal cases respectively.

CONCLUSION

The study fills a gap in the limited assessment of new vaccine introduction in DRC and the impact of the rotavirus vaccine on diarrheal disease. Overall, the findings do not identify a strong impact from rotavirus vaccine on diarrheal disease cases in the DRC, however limitations in the data suggest that more robust surveillance and additional data sources would be beneficial in future vaccine introduction analyses.

4.2 BACKGROUND

Rotaviruses are double-stranded RNA viruses, in the reovirus family; they are the leading cause for global deaths in children under the age of 5 years[60,61]. Symptoms of rotavirus are watery diarrhea and severe illness which can include fever, vomiting, abdominal pain, loss of appetite, and dehydration[61,62]. Viral loads can remain high in fecal matter and vomit for several days and transmission most often occurs via the oral-fecal route, although person to person and fomite transmission may also occur[61].

Globally, rotavirus illness is responsible for 450,000 deaths a year in children under the age of 5 years[63]. A 2015 study found that the majority of rotavirus-deaths that occurred globally were in sub-Saharan Africa and rotavirus caused 112.3 million episodes of diarrhea[64]. In the Democratic Republic of the Congo (DRC), rotavirus is estimated to account for 40-60% of diarrheal disease cases in children under 5[65–67]. According to the Rotavirus Accelerated Vaccine Introduction Network (RAVIN), the DRC has one of the highest rotavirus mortality rates, estimated in 2017 at 103 per 100,000 deaths[68,69].

Rotavirus is unique from other diarrheal diseases as it is not susceptible to traditional WASH strategies such as handwashing and clean water supplies, which is why the Rotavirus vaccine has become a key factor in the strategy to mitigate the diarrheal disease[62]. A systematic review and meta-analysis that evaluated the impact of rotavirus vaccine introduction in sub-Saharan Africa found that rotavirus vaccine introduction accounted for a significant reduction in the burden of diarrheal disease, dropping the proportion of rotavirus positive cases from 42% to 21%, and recommends the vaccine for national routine immunization systems.[63]

High disease burden and lack of control measures (outside of vaccination) have made rotavirus a priority disease to be controlled in the DRC. In January of 2020, the rotavirus vaccine, ROTASIIL, from India, was universally introduced in DRC, a delay from the planned phased rollout that was meant to start in October of 2019 in 4 provinces and expand[70 71]. ROTASIIL is a 3-dose oral vaccine that is administered at 6, 10 and 14 weeks which is the same dosing schedule as the OPV, pneumococcal and pentavalent (which includes Diphtheria, Pertussis, Tetanus, Hepatitis B and Hib) vaccines which are part of the standard RI schedule[72]. The introduction of the rotavirus vaccine has been collaboratively financed by Gavi, the vaccine alliance and the Congolese government and is the first Gavi supported implementation of the heat-stable rotavirus vaccine on the African continent [70]. In the DRC, it is estimated that 60% of diarrheal disease cases are caused by rotavirus, thus even post vaccine introduction, it is expected that there will continue to be diarrheal cases reported[65]. Diarrheal cases are expected to continue in DRC, particularly because of existing challenges with other diseases such as Cholera that cause diarrheal cases. A study by Ingelbeen et al. identified major hot spots for recurrent Cholera outbreaks in DRC from 2008-2017, mostly in the eastern regions of the country (Supplementary Figure 4), where we see a majority of diarrheal cases in DRC in general (Figure 9)[73].

In order to continue strengthening the RI system, the DRC Expanded Programme for Immunization (EPI) plans the introduction of new vaccines in tandem with system strengthening activities. When introducing a new vaccine, it is critical to identify the strengths and weaknesses of the existing health system and identify places that can be supported and strengthened through the process of introducing a new vaccine[22]. The EPI has launched a policy to revitalize the routine immunization system called the Mashako Plan, which began a little over a year before the rotavirus vaccine was added to the RI immunization schedule. This plan was initially implemented in

October 2018, as a collaboration between the DRC government and international partners. The plan was implemented in 9 initial provinces in 2018, an additional 9 provinces at the end of 2020 and the final 8 provinces between 2021 and 2022[23]. This strategy aimed to strengthen aspects of the following areas: immunization sessions held, supervisions visits conducted, monitoring and evaluation, vaccine availability and stock out reduction and funding[23]. As a part of the Mashako Plan, improved monitoring and access to vaccinations were key targets. The Mashako Plan targets the accessibility aspect of the RI system and demonstrates improvements in number of immunization sessions held and vaccine stock available at facilities. An article by Jamka et al. that discusses prior vaccine introductions and their role in the roll out of a new vaccine introduction focuses on the importance of collaboration, education to address hesitancy, ensuring equity in vaccine access and monitoring and evaluation in new vaccine introduction[74]. The Mashako plans aims to strengthen many of these aspects including vaccine access, equity and monitoring and evaluation. Similarly, an article by Malande et al. examines the barriers to vaccine uptake in rural parts of Uganda and identifies key barriers including knowledge and awareness, mistrust of vaccines, financial barriers, limited access to facilities and vaccine supply issues[75]. Although the Mashako Plan may not address some of these behavioral barriers, it aims to improve the logistical accessibility of vaccines by enhancing vaccine delivery and inventory management, which is in line with the findings of Zaffran et al. regarding the critical role of vaccine supply and logistics in reaching communities in need[76]. Therefore, we hypothesized that the Mashako Plan's efforts may support a stronger rollout of the rotavirus vaccines in the targeted provinces.

Since the introduction of the rotavirus vaccine in DRC in January of 2020, limited assessment of the impact on diarrheal disease has been conducted. To the authors knowledge, there have not been any papers published about the introduction of a new vaccine to the RI system in DRC. This paper

aims to evaluate the impact of the rotavirus vaccine introduction on diarrheal disease cases in children under 5 years using a series of comparative interrupted time series (CITS) analyses in provinces that have implemented routine immunization revitalization strategies through the Mashako Plan, using provinces that did not yet implement the Mashako Plan as the control. We hypothesized that Mashako Plan provinces would see a greater decrease in childhood diarrheal cases after rotavirus vaccine introduction than non-Mashako Plan provinces due to the expanded efforts for revitalizing the RI system overall in these provinces.

4.3 METHODS

Data Source

This analysis was conducted in the DRC with data from the District Health Information Software 2 (DHIS2)[25]. The DHIS2 is an open-source web-based platform and the world's largest health management information system (HMIS) launched globally in 2009 and implemented in DRC in 2014[25]. Data is collected at the health facility level and digitized to provide data up to the national level.

Variables

Diarrheal cases are reported in DHIS2 in three categories: simple, dehydrated and severely dehydrated diarrheal cases. All types of diarrheal disease cases were analyzed to give the full view of the data available in the analyses. Administrative data from DHIS2 provides the total number of simple, dehydrated and severe dehydrated diarrheal cases in children under 5 years at each health facility each month. For the analyses, I adjusted to the Health Area population level of each facility per 10,000 children. These variables are found under data elements, A diarrhea, and A 1.7 simple diarrhea, A 1.7 dehydrated diarrhea, and A 1.7 severe dehydrated diarrhea[25].

Health facilities were included in the analyses from all provinces if they included complete data regarding province, health zone, and health area names, date information, health area level population estimates and case information for simple, dehydrated and severe dehydrated diarrhea (depending on the analysis). In total, monthly data was included from January 2018 to December 2020 for 8,536 unique health areas (out of 8,971) which contributed 853,488 individual monthly observations. see supplementary table 1 for health area estimates and population numbers.

In addition, data on administrative rotavirus vaccine coverage were also downloaded from the DHIS2, for the same time period, these variables are found under data elements, B Vaccination par strategie and B 8.4 Rota.[25]

Statistical Analysis

A preliminary PanelView plot (Figure 4) was generated to get a view of the data and an outcome by year plot for each outcome of interest, comparing Mashako and non- Mashako provinces was generated. In order to conduct the CITS analysis binary assignments of pre-rotavirus vaccine introduction and post-rotavirus vaccine introduction (T) were generated. A pre- and post-Plan Mashako policy binary variable (A) was also created.

To evaluate the effect of the rotavirus vaccine introduction on the diarrhea cases in children under 5, among Mashako provinces vs. non-Mashako provinces, we used a series of comparative interrupted time-series analyses. Specifically diarrheal disease cases reported from December 2018 to December of 2020. This time period was chosen so that there would not be additional provinces implementing the Mashako plan and therefore changing groups in the middle of the analysis.

A negative binomial regression was used to estimate the change in diarrheal diseases cases in children under 5 pre and post vaccine introduction, between Mashako and non-Mashako Plan provinces. The model includes the health area population estimates for children under 5 as an offset and seasonality as a covariate (Figure 2). All analyses were conducted in R[77].

For all analyses a negative binomial regression was used to account for overdispersion, and a Durbin-Watson test was conducted for autocorrelation. This test resulted in a DW estimate= 0.9915, p-value < 2.2e-16 indicating that autocorrelation is greater than 0 (Figure 3). Therefore, a Newey-West standard errors were used to adjust for autocorrelation.

These analyses were conducted with data from December of 2018 through December of 2020, using the following equation:

Equation: E(Y|A=a, T=t)]=log ($\beta_0 + \beta_A a + \beta_T t + \beta_{AT} at + \beta_S S + offset(\log(HApop_5))$)

β_0= intercept per 10,000 children under 5 years

β_A= Binary mashako plan (0=Not Mashako, 1=Mashako)

β_T=Binary rotavirus vaccine introduction (0=pre-rotavirus vaccine introduction, 1=post-rotavirus vaccine introduction)

β_{AT}= coefficient of interest, the causal effect of rotavirus vaccine introduction on diarrheal disease cases (simple, dehydrated and severe dehydrated)

β_S = Season (0=rainy season, 1=dry season)

Y= Simple Diarrheal Disease Cases in children under 5 years old in DRC

HApop5= estimated population under 5 years by health area- used as a rate per 10,000 in model

A secondary ITS analysis was conducted in which the dataset time-period was extended from January 2018 to March 2022. This analysis used the same negative binomial regression to estimate

the change in diarrheal disease cases in children under 5 pre and post rotavirus vaccine introduction, using the following equation:

Equation: E(Y|time, post, c)]= log ($\beta_0 + \beta_{Time} time + \beta_{Post} post + \beta_{Time*PosT} time * post + \beta_S S + \beta_M m + offset(\log(HApop_5))$)

β_0= intercept per 10,000 children under 5 years

β_{Post}=Binary rotavirus vaccine introduction (0=pre-rotavirus vaccine introduction, 1=post-rotavirus vaccine introduction)

β_{Time}=Time variable

$\beta_{Time*Post}$= coefficient of interest, the causal effect of rotavirus vaccine introduction on diarrheal disease cases (simple, dehydrated and severe dehydrated)

β_S = Season (0=rainy season, 1=dry season)

β_M = Mashako Implementation (1=yes, 0=no)

Y= Simple Diarrheal Disease Cases in children under 5 years old in DRC

HApop5= estimated population under 5 years by health area- used as a rate per 10,000 in model

In this model the health area population estimates for children under 5 are used as an offset and both seasonality and month of actual Mashako Plan implementation and included in the model as covariates (Table 2).

As a final sensitivity analysis, provincial level plots were run to observe trends at a sub-national level (Supplementary Figures 1-3).

Assumptions

In order to conduct CITS analyses we assume parallel trends, meaning that before the rotavirus vaccine introduction we assume that the trends in diarrheal disease cases are the same between

Mashako and non-Mashako provinces. The parallel trend plots for all primary outcomes of interest including simple, dehydrated and severe dehydrated can be found below (Figures 5). The common shock assumption assumes that there are no other factors occurring at the time of this study that would decrease diarrheal disease cases differentially between Mashako and non-Mashako provinces, this assumption is untestable and very hard to meet. Consistency assumes that the intervention is sufficiently well defined, and positivity assumes that all provinces are eligible to receive all levels of the exposure. The assumption of exogeneity assumes that there is no unmeasured time-varying confounder of rotavirus vaccine introduction and diarrheal disease cases in children. In addition, we assume that there is no model misspecification and no other sources of bias or time-varying uncontrolled confounding.

Ethics

This activity was determined to be exempt from IRB (IRB#22-001553) at UCLA and the data is available from the MoH in DRC upon request.

4.4 RESULTS

Between January 2018 and December 2020 8,536 health areas reported 6,926,447 cases of simple diarrhea, 1,321,194 cases of dehydrated diarrhea and 311,979 cases of severe diarrhea. Over the time period of January 2020 to December 2020 after the rotavirus vaccine was introduced, 2,907,812 initial doses of the rotavirus vaccine were administered in those same health areas.

This panelview plot (Figure 2) shows the distribution of the data by province. The controls are the non-Mashako provinces over time with mon_count=1 being January of 2018. The treated pre and post are the Plan Mashako provinces pre and post rotavirus vaccine introduction.

Table 1 shows the interaction terms and 95% confidence intervals, from the negative binomial regression, for simple, dehydrated and severe dehydrated diarrheal disease cases (Table 1). For the Non-Mashako group, the results suggest that the implementation of rotavirus vaccine introduction has a negative effect on the incidence of simple diarrhea cases (IRR=0.984), indicating a 1.3% reduction in the incidence of this type of diarrhea each month due to the introduction of the rotavirus vaccine. However, in the Mashako group, the IRR for simple diarrhea cases shows a small negative effect (IRR=0.999), indicating a 0.1% reduction in the incidence rate of simple diarrhea each month after rotavirus vaccine introduction is due to the vaccine introduction. However, this effect is not statistically significant as the 95% CI includes the null value of 1. Figure 6 shows the plots of these estimates over time, stratified by season. The diarrheal disease case trends are increasing slightly before the introduction of the vaccine and this trend continues after a slight drop at the time of the vaccine introduction in both Mashako and non-Mashako Plan provinces.

In Non-Mashako Plan provinces the effect on dehydrated diarrhea cases is negligible (IRR=1.001), indicating no significant change in the incidence rate of dehydrated diarrhea each month due to the introduction of the rotavirus vaccine. Similarly, in the Mashako Plan provinces, for dehydrated diarrhea cases, the interaction term shows a small positive effect (IRR=1.005), suggesting a slight increase (0.7%) in the incidence rate of this type of diarrhea each month due to the rotavirus vaccine introduction. However, this effect is also not statistically significant as the 95% CI includes the value of 1. In Figure 7, we see this increase in the slope of the Mashako Plan province line after the introduction of the vaccine.

Among the Non-Mashako Plan provinces, the effect on severe dehydrated diarrhea cases is also small and not significant (IRR=0.998), indicating no clear evidence of a change in the incidence rate of severe dehydrated diarrhea over time due to the rotavirus vaccine. Similarly, among the Mashako provinces, for severe dehydrated diarrhea cases, the interaction term shows a small negative effect (IRR=0.995), indicating a 0.4% reduction in the incidence rate of this type of diarrhea each month after rotavirus vaccine introduction. However, this effect is not statistically significant as the 95% CI includes the value of 1. Figure 8 plots the model stratified by season. We can see that there is a larger decrease is the non-Mashako provinces than the Mashako provinces.

Table 2 shows the results of an Interrupted Time Series (ITS) analysis that evaluates the impact of the rotavirus vaccine introduction on the incidence rates of different types of diarrhea in children under 5 years in the DRC. The analysis controlled for season and Mashako Plan implementation, covering the period between January 2018 and March 2022.

The incidence rate ratios (IRR) for simple and severe diarrhea are 0.989 (95% CI: 0.987, 0.990) and 0.993 (95% CI: 0.990, 0.996), respectively, indicating a minimal decrease in the incidence rates of these types of diarrhea after the introduction of the rotavirus vaccine (Table 2). The IRR for dehydrated diarrhea is 0.991 (95% CI: 0.982, 1.001), which crosses the null of 1, suggesting that the vaccine may not have a significant impact on the number of reported dehydrated diarrheal cases (Table 2).

4.5 DISCUSSION

In this paper, we present an assessment of the implementation of the rotavirus vaccine introduction on diarrheal disease cases in the DRC within the context of the Mashako Plan to revitalize the routine immunization system. From our results, we see the rate of simple diarrheal disease cases

increasing in children under 5 years until the introduction of the rotavirus vaccine in both Mashako and Non-Mashako Plan provinces. After rotavirus vaccine introduction, we observed an immediate drop in cases and then a slower rate of increase in simple diarrheal disease cases than before the introduction of the rotavirus vaccine. Because our outcome of interest is overall diarrheal disease cases (divided into 3 types) and not diarrheal disease cases specifically caused by rotavirus it makes sense that we may see no change or even an increase in cases due to other causes of diarrheal disease.

The Mashako Plan provinces appear to have a lower rate of diarrheal disease cases initially which is somewhat unsurprising because it includes 9 of 26 provinces that have received additional support and funding for routine immunization system strengthening activities, which likely improved the entire system, not only immunizations. For this same reason while we do see a drop in the rate of diarrheal disease cases it is not surprising that it is smaller than among the control non-Mashako provinces.

While our study saw minimal to no variation in our result by season (Figures 6-8), a similar time-series analysis of the relationship between diarrhea in children and rotavirus in Ghana found that seasonal variation influences diarrheal cases and there are less diarrheal cases recorded when more children are vaccinated with the rotavirus vaccine [78]. A 2020 study that looked at acute diarrheal cases in Lubumbashi, DRC found that out of all cases of acute diarrhea, 45.3% tested positive for rotavirus[67]. Similarly, another study in Bukavu, Sud-Kivu, DRC found a similar rotavirus prevalence of 42.6%[66]. Lubumbashi and Bukavu are both located in eastern Congo and these are the regions of the country with ongoing Cholera outbreaks which means that this estimate of 42-45% of the cases being caused by rotavirus may be an underestimate for other parts of the country.

Similarly, a recent study published in 2022 by Luhata et al. evaluated children under the age of 5 at 3 sentinel surveillance sites admitted for gastroenteritis, found that rotavirus positivity was 60%[65]. In this study 2 of the 3 sites were in Kinshasa and the last was in Tshopo. These regions are less likely to have Cholera outbreaks and therefore testing getting a higher positivity rate for rotavirus here makes sense. These studies demonstrate that a significant proportion of diarrheal disease cases in DRC can be attributed to rotavirus and align with the decision to add rotavirus vaccine to the DRC routine immunization system. However, it is important to note that it is possible that there be geographic differences throughout the country.

A similar study in Kenya evaluated the introduction of the Rotavirus vaccine on hospital admissions for diarrhea among children, using a controlled interrupted time series analysis, and found a vast decrease in the number of hospitalizations[79]. Unlike our study which used administrative data from the entire country, this study focused on 2 population-based surveillance sites to evaluate the impact of the vaccine using hospital-based surveillance data[79]. This study used rotavirus negative hospitalizations as the controls for the analysis and included stool sample testing to confirm rotavirus in the cases[79]. Our study does not include the specific cause of the diarrheal disease cases and therefore this type of control group was not possible for our analysis. The introduction of the Mashako Plan to revitalize routine immunization in DRC provided a unique lens for comparison. Because this policy was implemented in some provinces, but not all nearly two years before the introduction of the rotavirus vaccine we were able to use the non-Mashako provinces as a control group to evaluate the introduction of the rotavirus vaccine within the context of this larger vaccination system strengthening policy (Mashako Plan).

There are many logistical, political, and financial challenges to introducing a new vaccine to the routine immunization system, particularly in a country as large, geographically and culturally diverse as the DRC. New vaccine introduction into a routine immunization system depends on many factors including affordability, cost-effectiveness, vaccine availability, safety, disease burden and suitability for the country[80]. A key factor that can determine if a country has the ability to introduce a new vaccine into the routine system is affordability. Typically, GAVI specifically works to provide a funding mechanism for vaccines in low- and middle-income countries (LMICs) to increase access to life saving vaccines[81]. In our analysis somewhat addressed these factors by using the Mashako Plan as a proxy for political will to support vaccination and financial and logistic resources to support the RI system.

The introduction of a new vaccine requires careful consideration of multiple factors. In addition to the disease burden and cost, immunization programs must evaluate if their systems meet the seven benchmarks outlined by the World Health Organization (WHO) and The Strategic Advisory Group of Experts on Immunization (SAGE). These benchmarks include a strong decision-making and accountability process, a well-performing routine immunization system, a well-trained and motivated workforce, functional logistics, cold chain and vaccine management, safe immunization practices and tracking of adverse events, high-quality surveillance and coverage monitoring, and a financially sustainable system. Immunization leaders must also determine the scope of the new vaccine introduction, age groups to target, whether catch-up visits are needed, and vaccine formulations, storage, cold chain, and transport requirements[22].

Strengths

The strengths of this study include a large sample size that includes all provinces of DRC including data from over 8,000 health areas with over 800,000 observations, providing a comprehensive picture of diarrheal disease cases in the country. To the authors knowledge this is the first paper to attempt to evaluate the introduction of a new vaccine into the RI system in DRC. This perspective provides essential information for what changes need to be made to the surveillance and evaluation systems to properly to assess the effectiveness of new vaccines as they are added to the RI system. The use of a control group of non-Mashako Plan provinces allowed for the evaluation of the introduction of the rotavirus vaccine within the context of a larger vaccination system strengthening policy (Mashako Plan). The study's time-series analysis of diarrheal disease cases allows for the observation of trends over time, and the inclusion of different types of diarrheal disease cases provides a more nuanced understanding of the impact of the rotavirus vaccine. The study also highlights the challenges of introducing a new vaccine into a routine immunization system in a LMIC like the DRC, and the need to consider multiple factors, including disease burden, cost, and the seven benchmarks outlined by the WHO and The SAGE on Immunization.

Limitations

Beyond the previously discussed assumptions of parallel trends, common-shock events and modeling biases, this study design is limited because of the nature of population level data and potential for ecological fallacy. DHIS2 data by nature has issues with missing values, delayed reporting, and over-estimation of estimates due to incorrect population numbers. Because we are interested in look at the outcome of diarrheal disease, we are making the assumption that during the same time period there were no other major activities that would have significantly reduced diarrheal disease cases during this time period. We know that only 45-60% of diarrheal disease cases are estimated to be caused by rotavirus in DRC and therefore it is feasible that any reduction

in cases caused by the rotavirus vaccine is being masked by another cause of diarrheal disease. Particularly in the eastern provinces there are ongoing challenges with cholera outbreaks that geographically coincide with provinces where we see higher levels of diarrheal cases such as North and South Kivu. A study by Ingelbeen et al. examines the cholera outbreaks in the DRC from 2008-2017 and found an increase in cases in 2017[73]. Most of these cases occurred along "hot zones" for Cholera on the eastern border provinces of DRC which are some of the same provinces where we see increased case levels of diarrhea in our provincial estimate plots (Supplementary Figure 1-4)[73].

While we did adjust for the dry season from May to September which is cooler and generally sees an uptick in diarrheal disease cases, as noted in the article by Luhata et al., we were unable to control for the variation in seasonality regionally or vaccine stock outs[65]. In addition, although it is common knowledge that there are security issues in the east of the country, the only available data classifying health areas is static and therefore could not be included as a time-varying covariate.

Another significant limitation to this analysis is the availability of DHIS2 data by age. For this set of analyses, we are assessing the impact of the rotavirus vaccine introduction on diarrheal disease cases, comparing Mashako to non-Mashako Plan provinces in DRC. In DHIS2 diarrheal disease case information is only available for children <5 years; this makes the evaluation of new vaccine introduction particularly difficult because the new vaccine introduction only targets children under 11 months. By analyzing the data with children up to 5 it may take 4 to 5 years to actually see a the impact of the vaccine on diarrheal cases because the impact is being diluted by unvaccinated older children. There is diarrheal disease information available in Integrated Disease Surveillance

and Response (IDSR) for <11 months of age in DRC, but the data for this variable was not collected until January 2020 which is when the rotavirus vaccine was introduced, therefore it cannot give you any information about before vaccine introduction.

Another limitation of this analysis is the lack of information presently available about vaccine stock for rotavirus vaccine at each facility over this time period. Without accounting for stock outs in certain health areas we may be underestimating the impact of the rotavirus vaccine on diarrheal disease cases as it may not have been available to some during this time despite officially being part of the routine immunization system.

The initial 9 Mashako Plan provinces were selected because they had the largest population, accounted for 45% of under immunized children in DRC, faced challenges with vaccine stock outs and were identified as the most vulnerable provinces of the 26[23]. The identification criteria for these provinces was not random and therefore the remaining control provinces, represent provinces with less challenges in the RI system, smaller populations, less stock outs of vaccines and are less vulnerable. Using these provinces as controls likely caused us to underestimate or mask the impact of the Mashako Plan on the success of rotavirus vaccine introduction in those provinces. Additionally, the Mashako Plan was not randomly assigned to provinces and implementation of the policy was informed by baseline numbers, pre-policy intervention. In supplementary table 1, province details including population are outlined and in supplementary Figures 1-3, provincial levels plots of diarrheal case data show variation between provinces.

Conditional exogeneity cannot be met because the rotavirus vaccine was introduced because of high rates of diarrheal disease, of which a majority (~60%) are estimated to be caused by rotavirus. This study is also limited by the data available for the analysis. In order to conduct a CITS only

one year of data after rotavirus vaccine introduction was able to be used because many of the control provinces began implementation of the Mashako plan in 2021. For this reason, an ITS analysis was also conducted that covers a longer period of time and controls for Mashako implementation month.

4.6 CONCLUSION

Unlike we hypothesized the results from this study suggest a minimal change in the rate of diarrheal disease cases in children under 5 in DRC in the non-Mashako and Mashako provinces. We do see a lower starting rate of diarrheal disease within the Mashako provinces. We see an initial drop in the rate of diarrheal cases at the introduction of the rotavirus vaccine which is in line with other studies that have evaluated the effect of the rotavirus vaccine on diarrheal disease cases. This study is unique in that it attempts to evaluate the impact of the rotavirus vaccine introduction on diarrheal diseases cases in children across the DRC, however it is limited by the inability to verify causes of cases with lab confirmation. It is also limited because, the lowest age group available to evaluate diarrheal disease cases in DHIS2 is children under 5, however the rotavirus vaccine campaign targeted children under 11 months. Therefore, we may not be able to see the true impact of the vaccine introduction until the entire under 5 cohort is vaccinated, five years from vaccine introduction. IDSR data on diarrheal disease cases in children 0-11 months was collected starting in January of 2020. Unfortunately, this does not allow for any pre-vaccine comparison. As DRC plans the introduction of new vaccines such as the Human Papilloma Virus (Vaccine) and Typhoid it would be advantageous to introduce surveillance programs several years prior to the vaccine introduction. The results of this study may inform future assessments of the overall impact of the rotavirus vaccine on childhood diarrheal cases in the DRC and policy decisions related to new vaccine introduction.

This study has important policy implications for DRC because it demonstrates the need for both a strong routine immunization platform and a strong surveillance system to support new vaccine introductions. This is the first attempt to evaluate a new vaccine introduction into the RI system in DRC. The challenges and limitations faced in conducting these analyses can provide insights into the type of surveillance and evaluation measures that will help other countries facilitate successful new vaccine introductions and evaluations. Diarrheal cases are one of the top factors for mortality in children under 5 years of age and outcomes from this study may inform both the DRC MOH and others future work within the country and beyond.

Tables and Figures

Figure 1. Map of initial 9 Mashako Plan Provinces

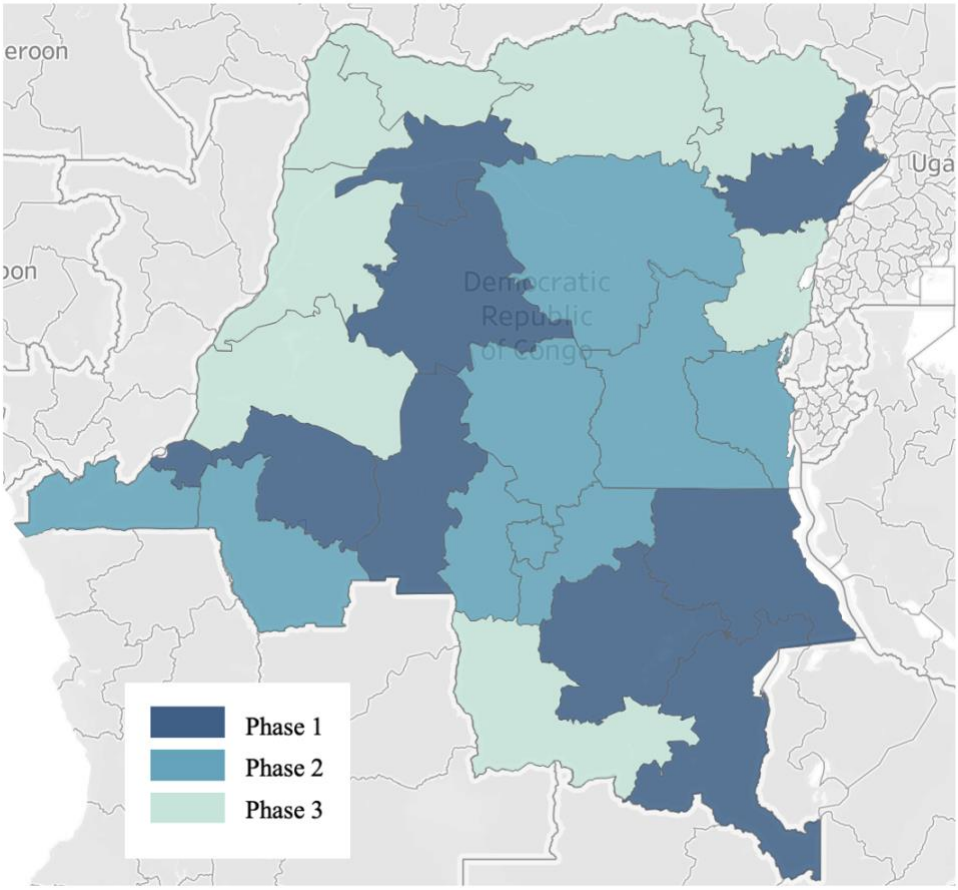
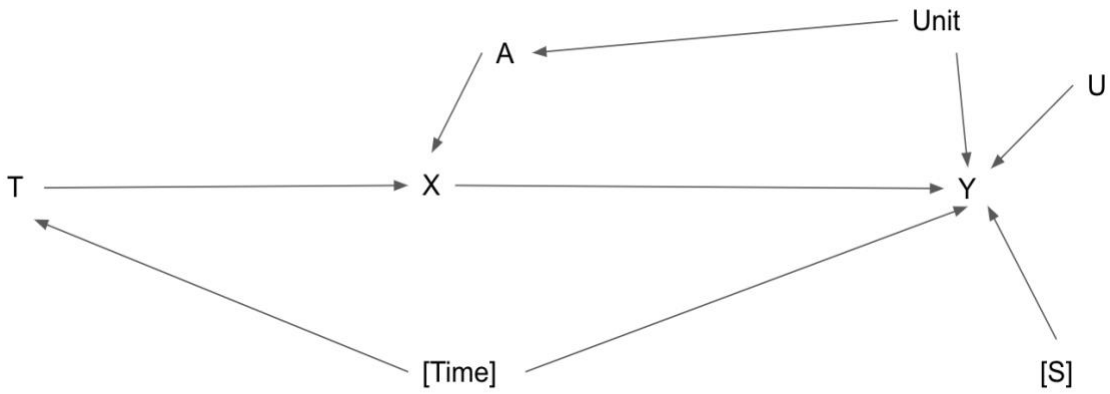
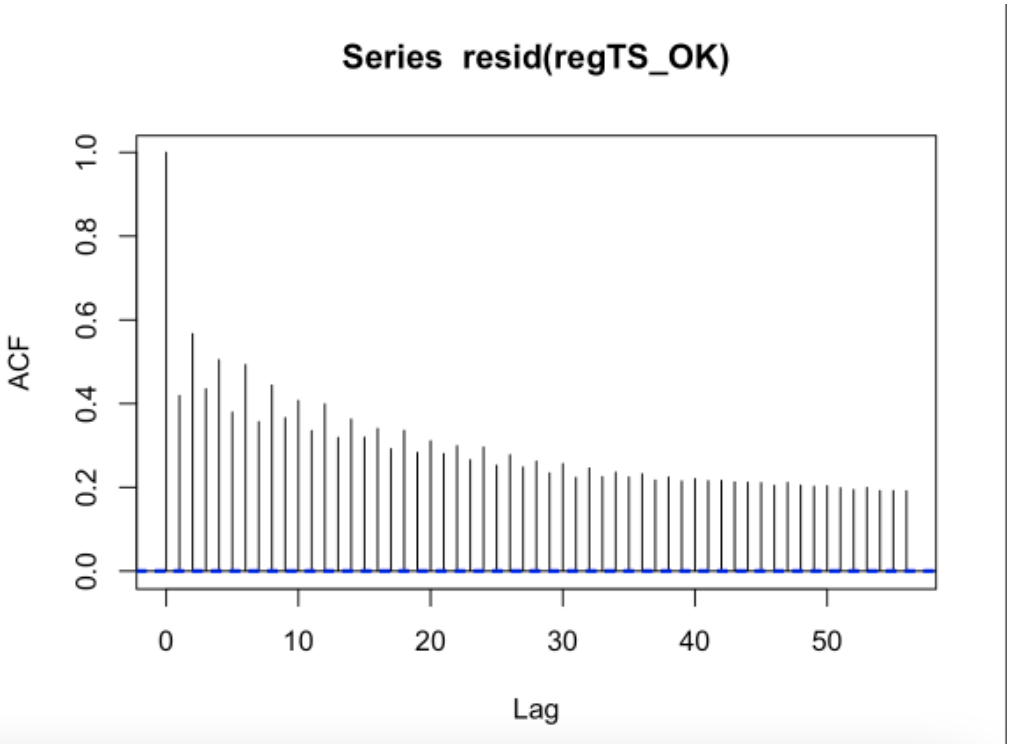


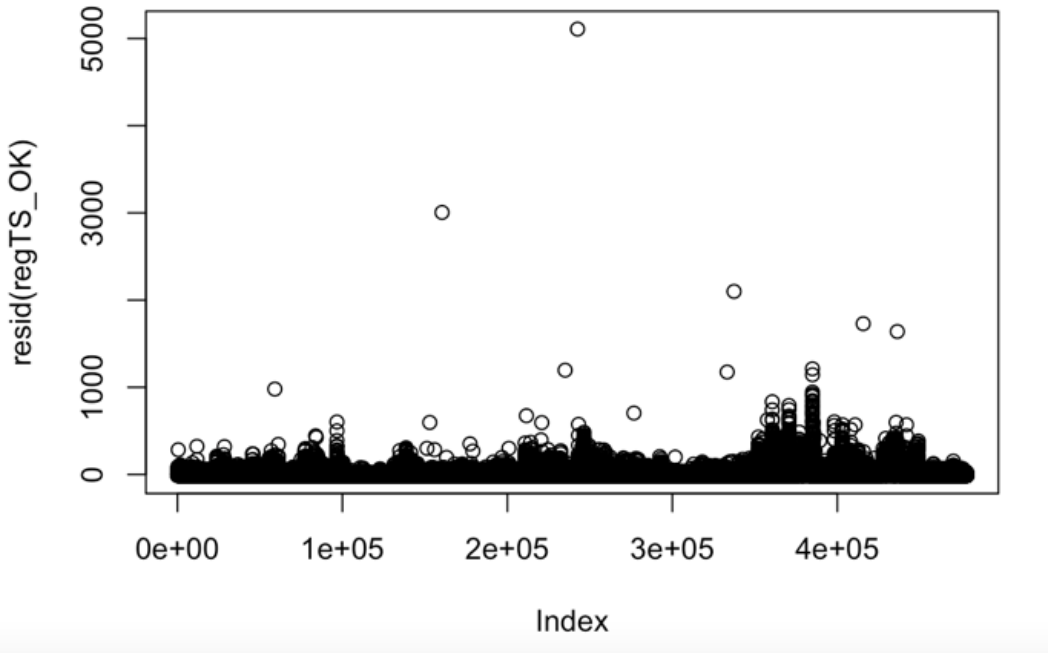
Figure 2. DAG



Time= month
T= Before (T=0) or After (T=1) Rotavirus vaccine introduction (post)
A= Plan Mashako (A=1) vs non-Plan Mashako (A=0) Provinces (treated)
X= A*T (treated*post)
Y= Diarrheal disease cases
Unit= Province
S=Seasons (1=Dry, 0=Rainy)
U= Unknown

Figure 3. Autocorrelation Test Plots





Preliminary Plots

Figure 4. Panelview plot

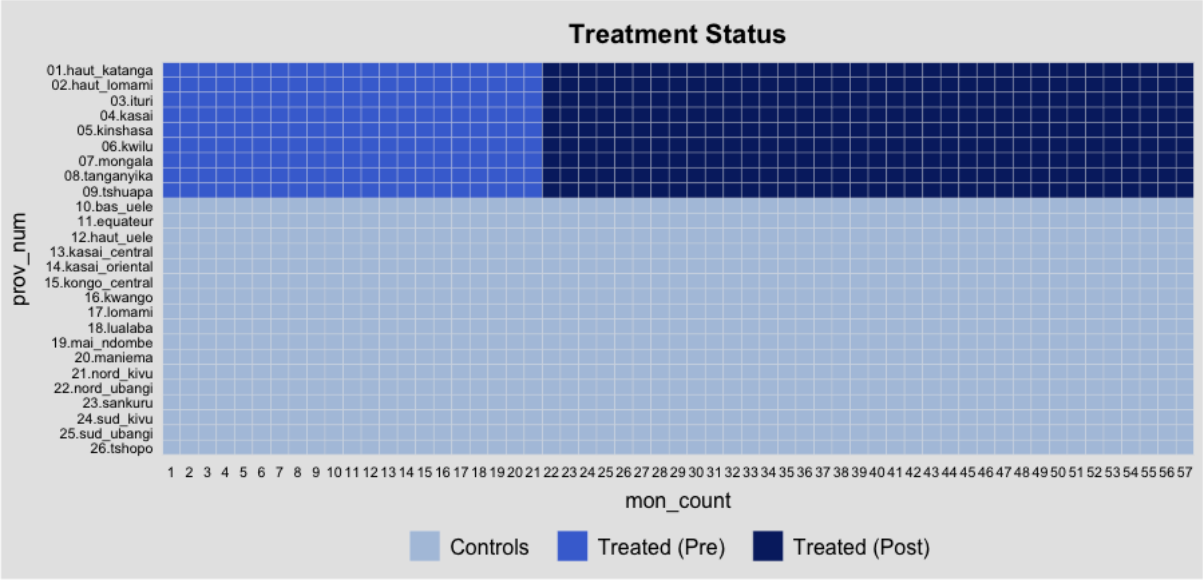


Figure 5. Parallel Trend Plots

Figure 5a

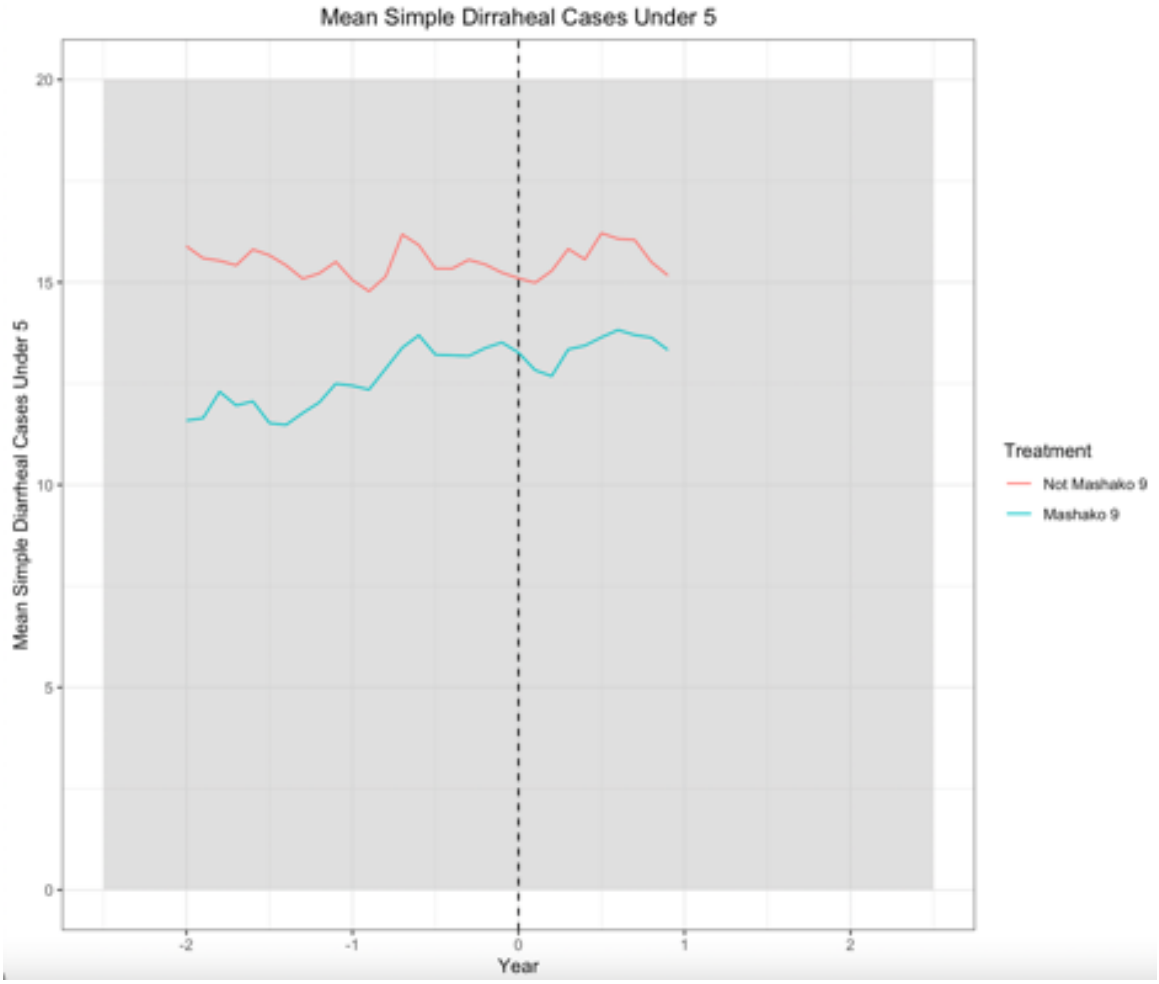
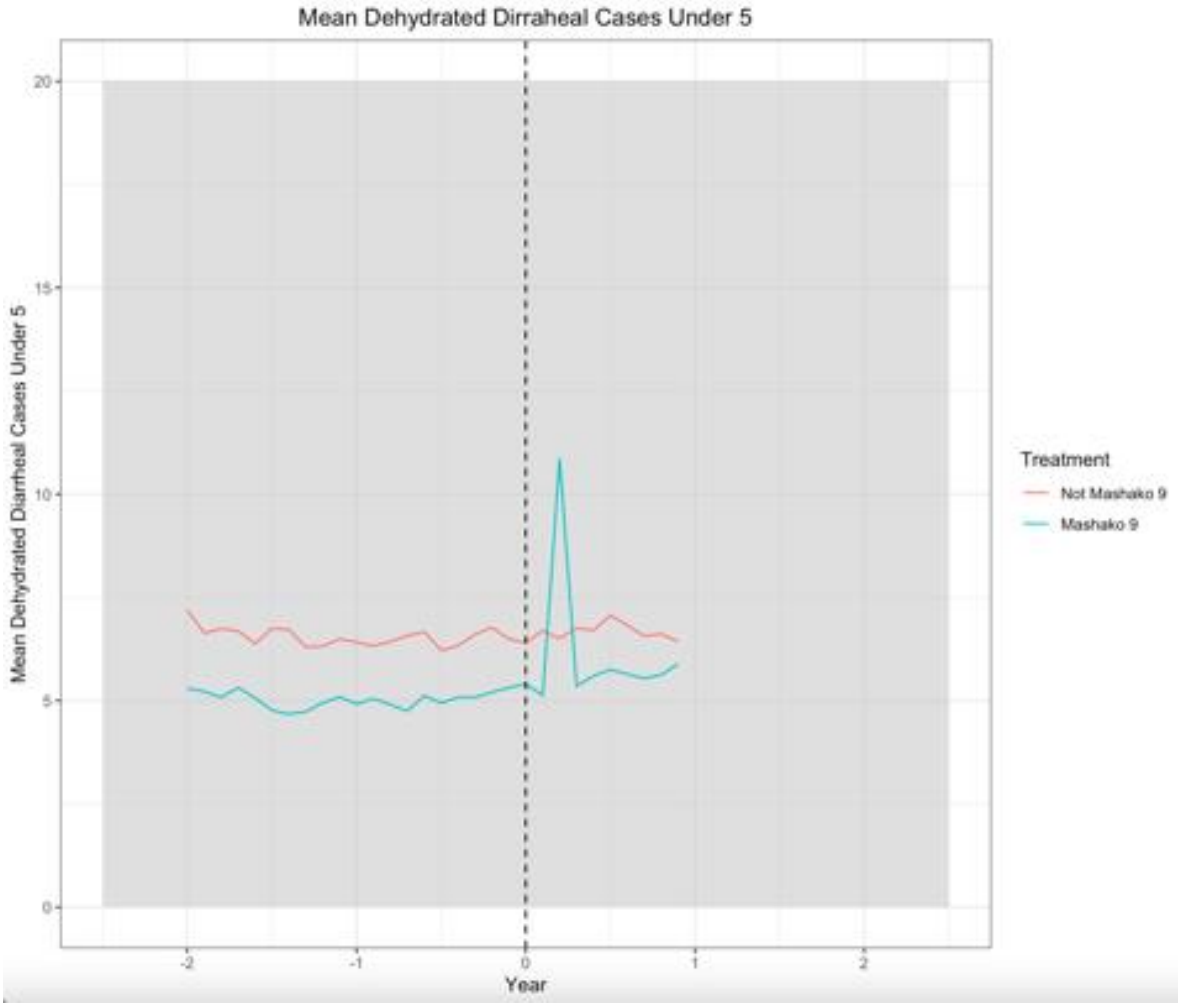


Figure 5b


Mean Dehydrated Dirraheal Cases Under 5
Mean Dehydrated Diarrheal Cases Under 5
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5
0
-2
-1
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1
2
Year
Treatment
Not Mashako 9
Mashako 9

Figure 5c

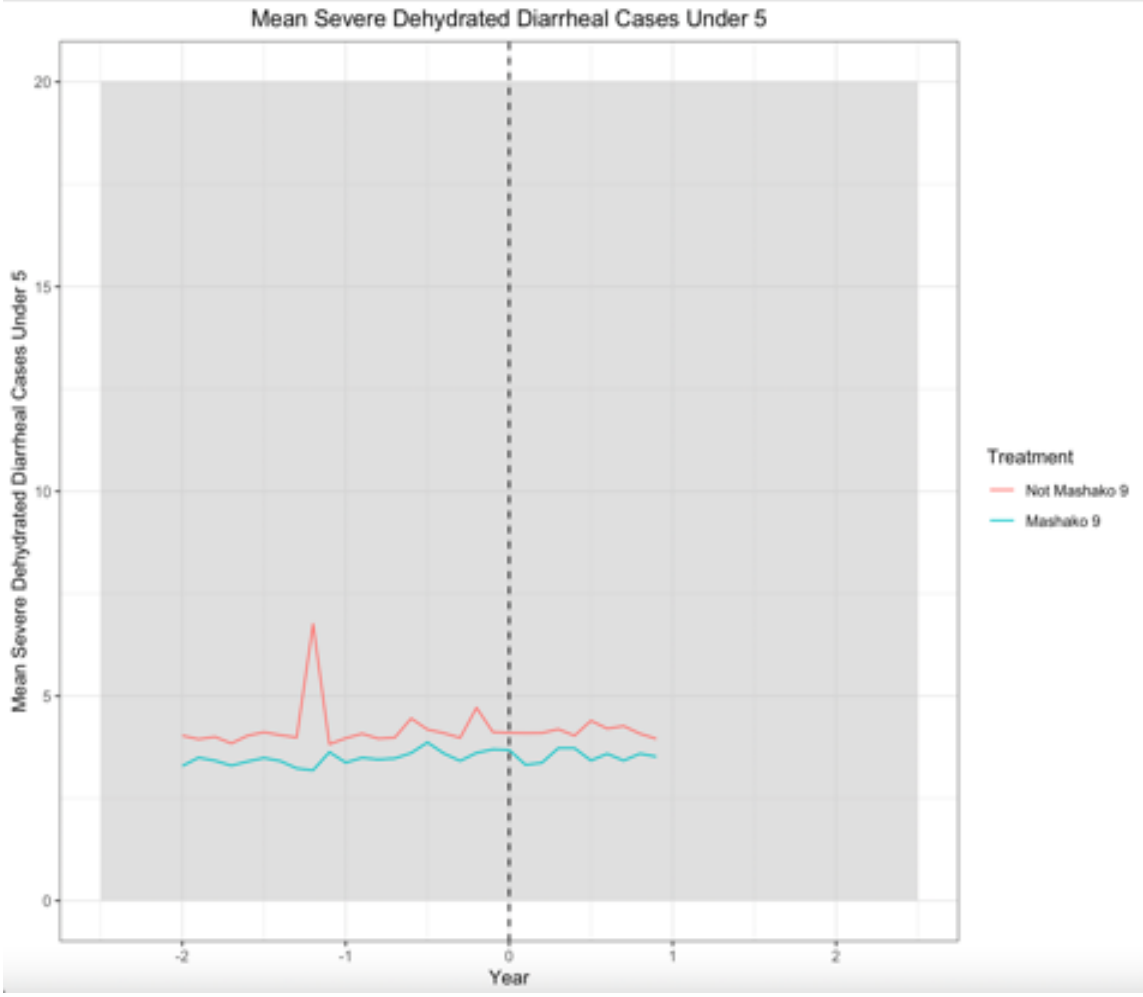

Mean Severe Dehydrated Diarrheal Cases Under 5
Mean Severe Dehydrated Diarrheal Cases Under 5
20
15
10
5
0
-2
-1
0
1
2
Year
Treatment
Not Mashako 9
Mashako 9

Table 1. Results of Comparative Interrupted Time Series Analyses for Simple, Dehydrated and Severe Dehydrated Diarrheal Cases in Children under 5 years, per 10,000 population

		Simple Diarrhea Cases		**Dehydrated Diarrhea Cases**		**Severe Dehydrated Diarrhea Cases**	
		IRR	**95%CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Non-Mashako	**Time*Rotavirus Vaccine Implemented (Interaction term)**	0.984	(0.980, 0.989)	1.001	(0.994, 1.009)	0.998	(0.980, 1.017)
Mashako	**Time*Rotavirus Vaccine Implemented (Interaction term)**	0.999	(0.990, 1.007)	1.005	(0.995, 1.016)	0.995	(0.981, 1.008)

Figure 6. Comparative Interrupted Time Series Analysis for outcome Simple Diarrheal Disease cases per 10,000 population in children under 5 years, stratified by season (rainy season=0, dry season=1)

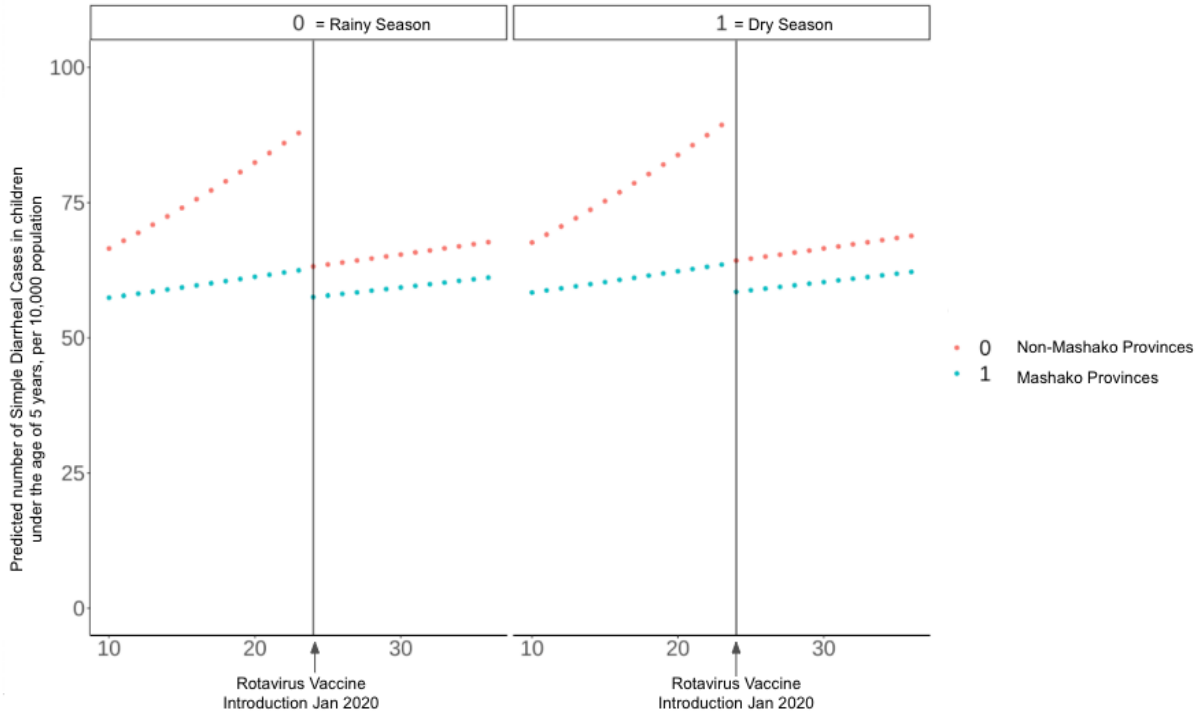


Figure 7. Comparative Interrupted Time Series Analysis of Dehydrated Diarrheal Disease Cases (Mashako vs. Non-Mashako) in children under 5 years, per 10,000 population, stratified by season

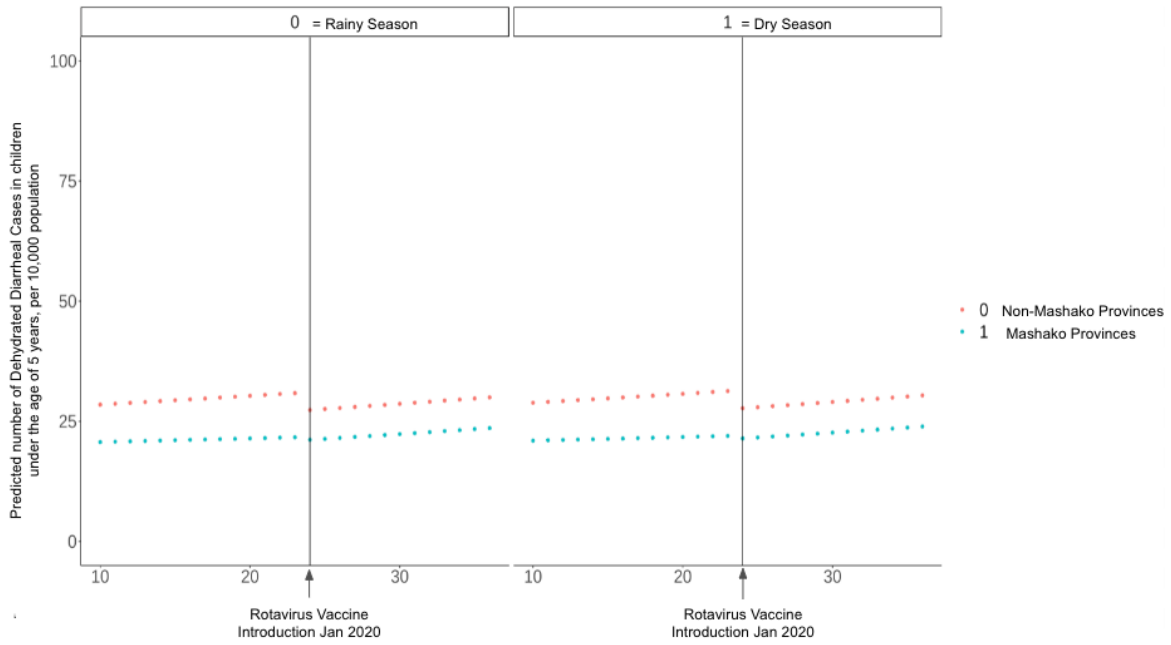


Figure 8. Comparative Interrupted Time Series Analysis of Severe Dehydrated Diarrhea, stratified by Season (0=Rainy Season, 1=Dry Season)

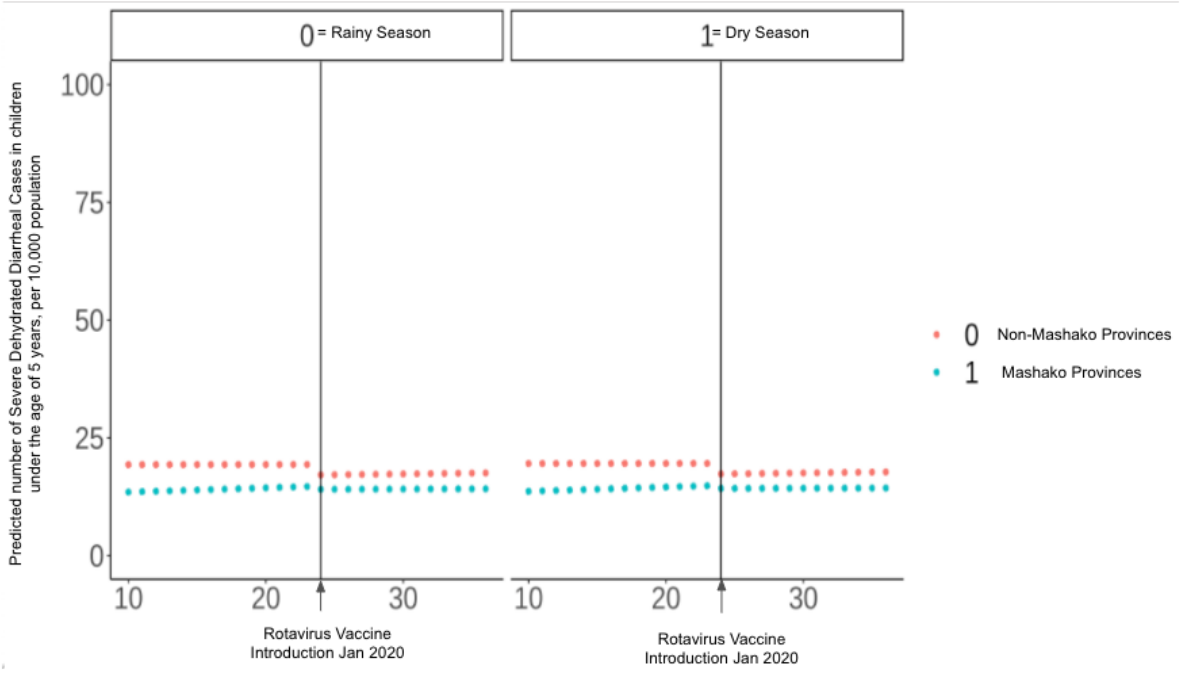


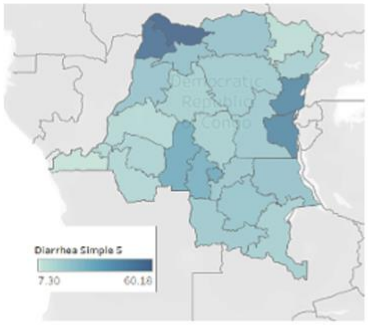
Table 2. Expanded ITS Analyses, Rotavirus vaccine introduction event of interest (January 2020), controlling for season and Mashako plan implementation, January 2018-March 2022

	Simple Diarrhea		Dehydrated Diarrhea		Severe Diarrhea	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Interaction term (Time*Rota Implemented)	0.989	(0.987, 0.990)	0.991	(0.982, 1.001)	0.993	(0.990, 0.996)

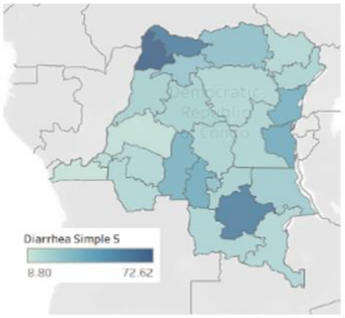
*Seasonality, Mashako implementation month controlled for in the model

Figure 9. Maps of Diarrheal Disease Cases Over Time: a. Simple Diarrheal Disease Cases b. Dehydrated Diarrheal Disease Cases c. Severely Dehydrated Diarrheal Disease Cases

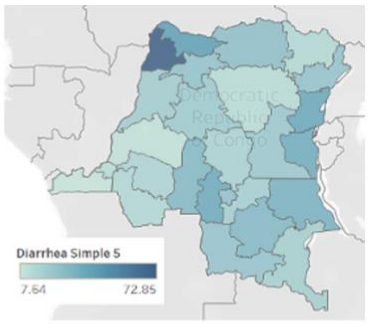
Figure 9a.



Simple Diarrhea Cases 2018

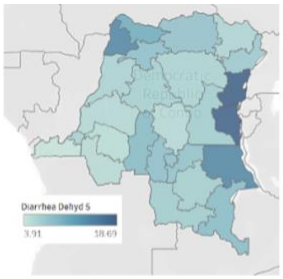


Simple Diarrhea Cases 2019

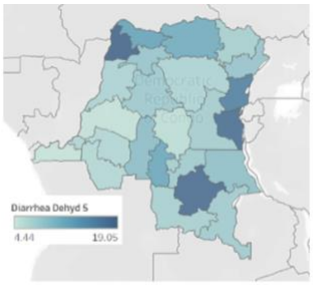


Simple Diarrhea Cases 2020

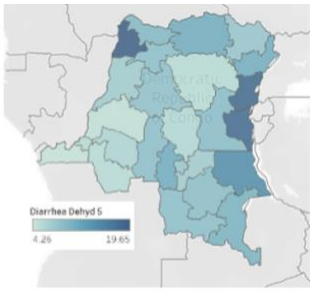
Figure 9b.



Dehydrated Diarrheal Cases 2018



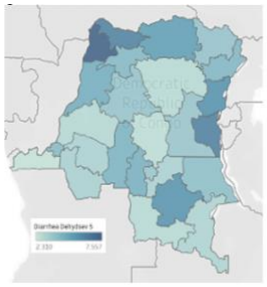
Dehydrated Diarrheal Cases 2019



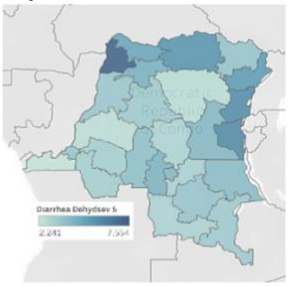
Dehydrated Diarrheal Cases 2020

Figure 9c.

Severe Dehydrated Diarrheal Cases 2018



Severe Dehydrated Diarrheal Cases 2019



Severe Dehydrated Diarrheal Cases 2020

Supplementary Tables/Figures

Table 1: Province Details for All Provinces

Province	Mashako Implementation Phase	Province Population 2020	# of Health Zones	# of Health Areas	# of Health Facilities
Haut-Katanga	1	5,936,831	27	386	987
Haut-Lomami	1	4,709,707	16	334	529
Ituri	1	6,073,936	36	562	997
Kwilu	1	5,352,224	24	581	1015
Kinshasa	1	9,484,960	35	395	928
Kasaï	1	4,901,461	18	396	988
Mongala	1	2,604,511	12	293	491
Tanganyika	1	3,190,800	11	267	305
Tshuapa	1	2,220,863	12	242	439
Kongo-Central	2	4,119,650	26	391	1377
Kasaï-Oriental	2	5,285,640	18	326	570
Kwango	2	2,707,404	14	266	541
Kasaï-Central	2	4,977,887	16	432	813
Lomami	2	4,290,171	14	316	719
Maniema	2	2,653,912	12	282	534
Sud-Kivu	2	7,380,837	18	635	985
Sankuru	2	2,374,334	34	248	463
Tshopo	2	3,682,227	11	420	671

Mai-Ndombe	3	1,964,133	16	310	602
Sud-Ubangi	3	3,298,690	11	246	371
Équateur	3	2,657,834	23	286	493
Nord-Ubangi	3	1,626,060	12	169	214
Bas-Uele	3	1,368,138	519	162	175
Haut-Uele	3	1,894,399	13	211	504
Nord-Kivu	3	9,132,303	34	582	919
Lualaba	3	2,657,266	14	233	423
Total		106,546,179	519	8,971	17,053

Figure 1. Provincial Plots of simple diarrheal disease cases over time: a. Plots of Simple Diarrheal Disease cases over time in Non-Mashako Provinces, b. Plots of Simple Diarrheal Disease cases over time in Mashako Provinces

Figure 1a

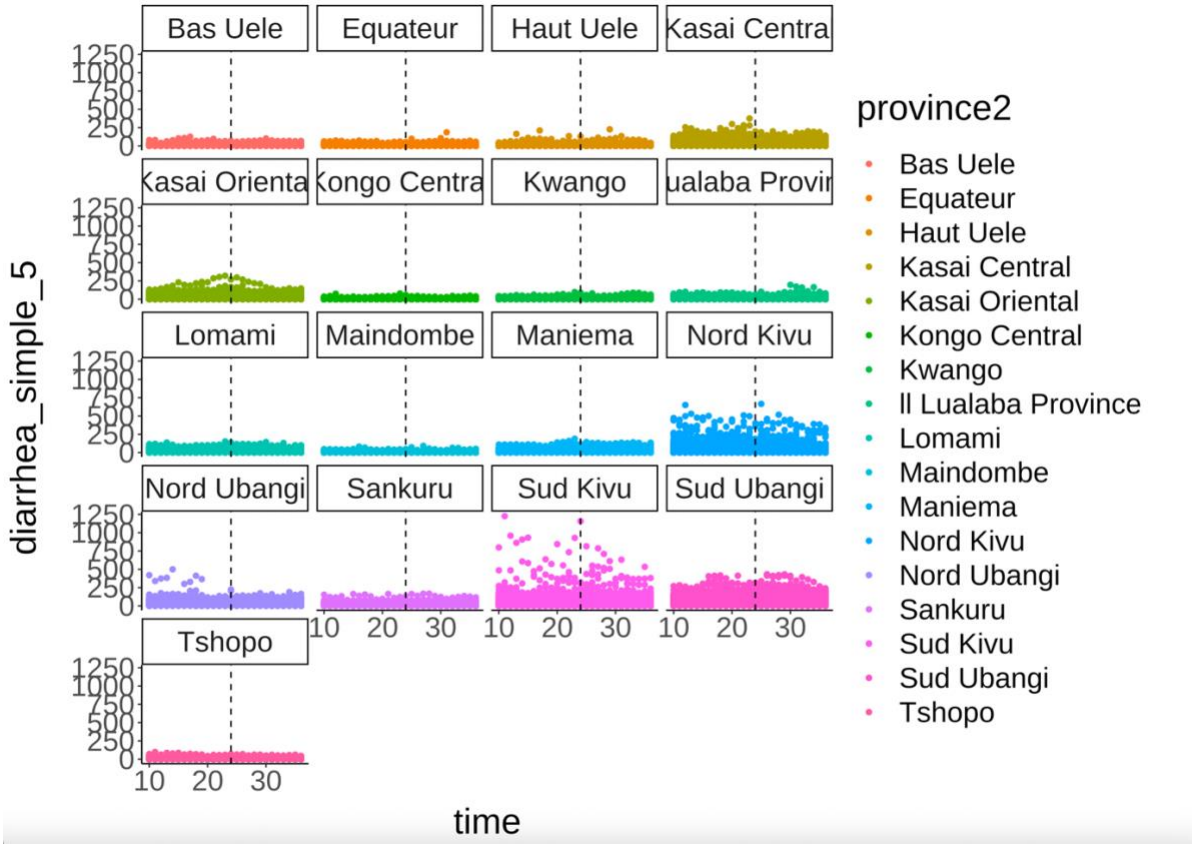
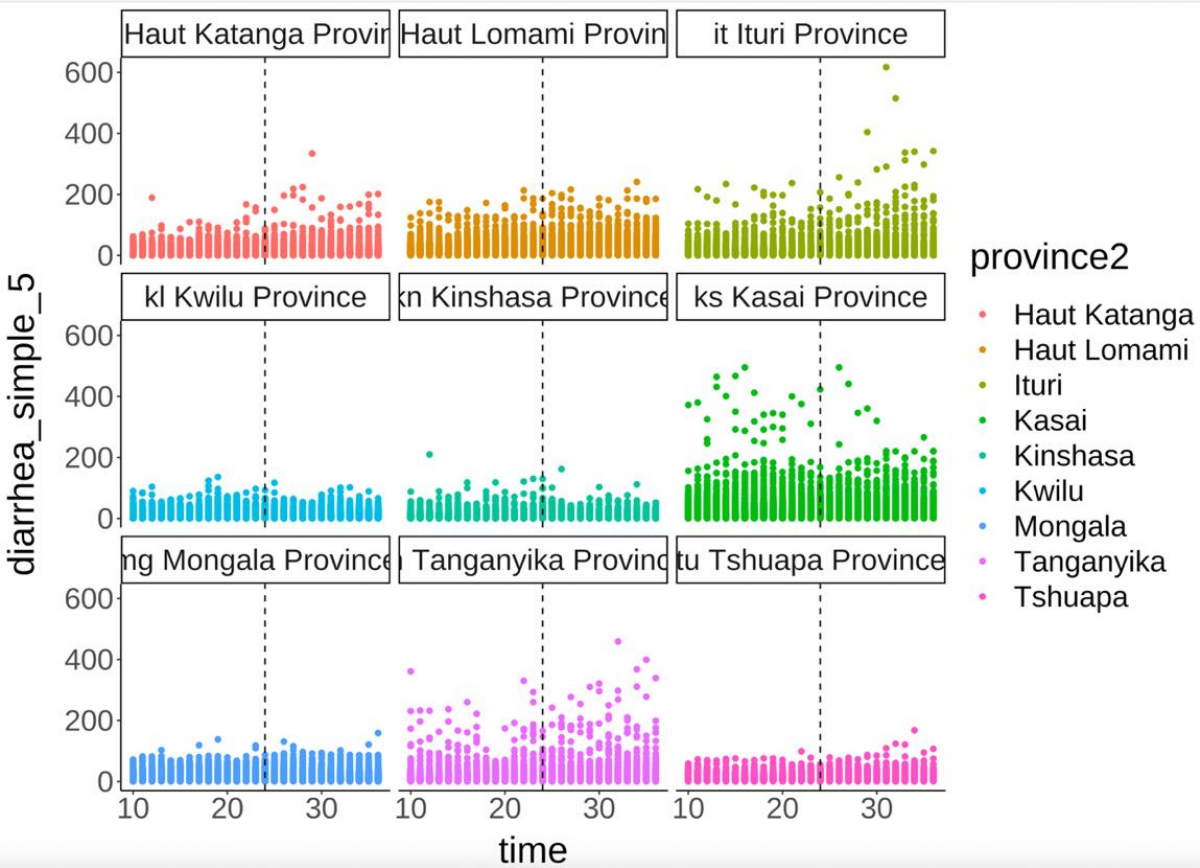


Figure 1b


Haut Katanga Provir
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kl Kwilu Province
kn Kinshasa Province
ks Kasai Province
ng Mongala Province
Tanganyika Provinc
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Ituri
Kasai
Kinshasa
Kwilu
Mongala
Tanganyika
Tshuapa

Figure 2. Provincial Plots of dehydrated diarrheal disease cases over time**:** a. Plots of Dehydrated Diarrheal Disease cases over time in Non-Mashako Provinces, b. Plots of Dehydrated Diarrheal Disease cases over time in Mashako Province

Figure 2a

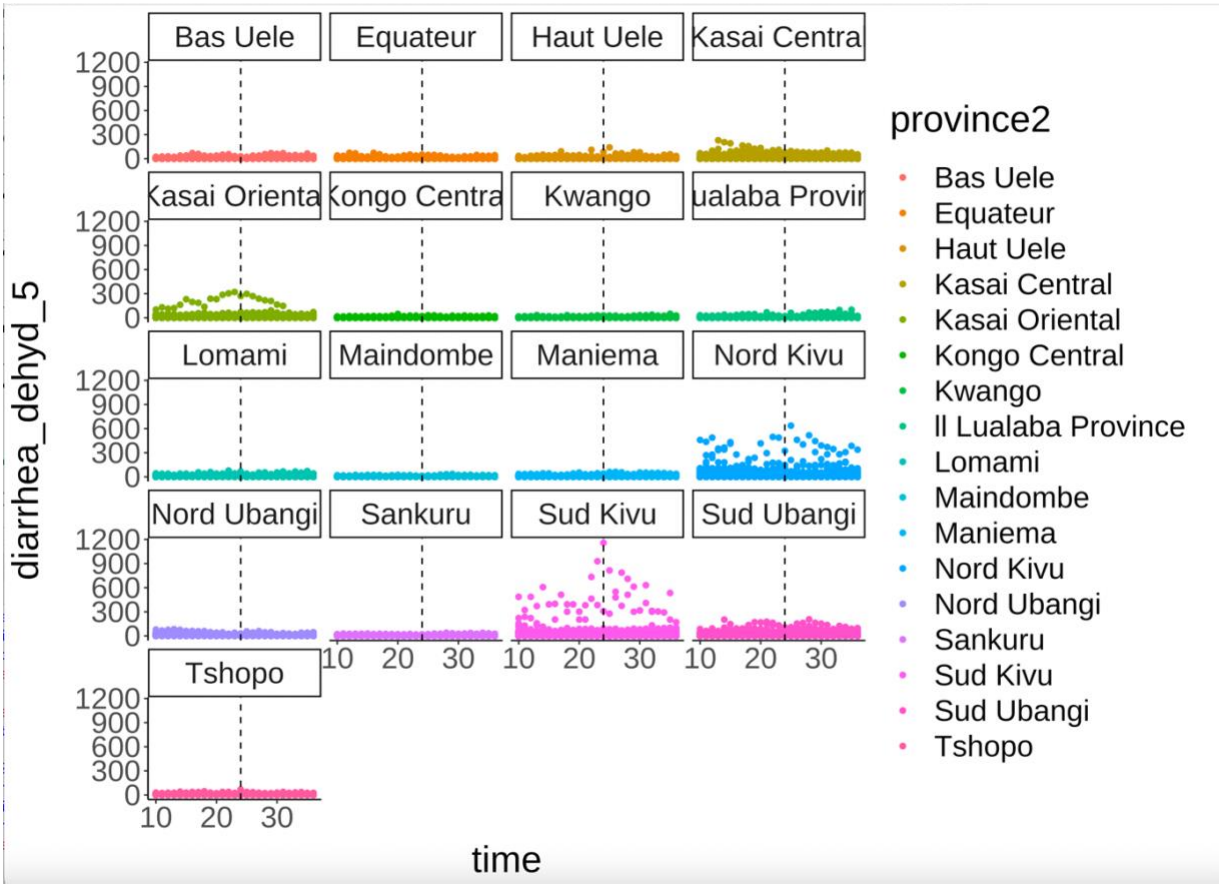
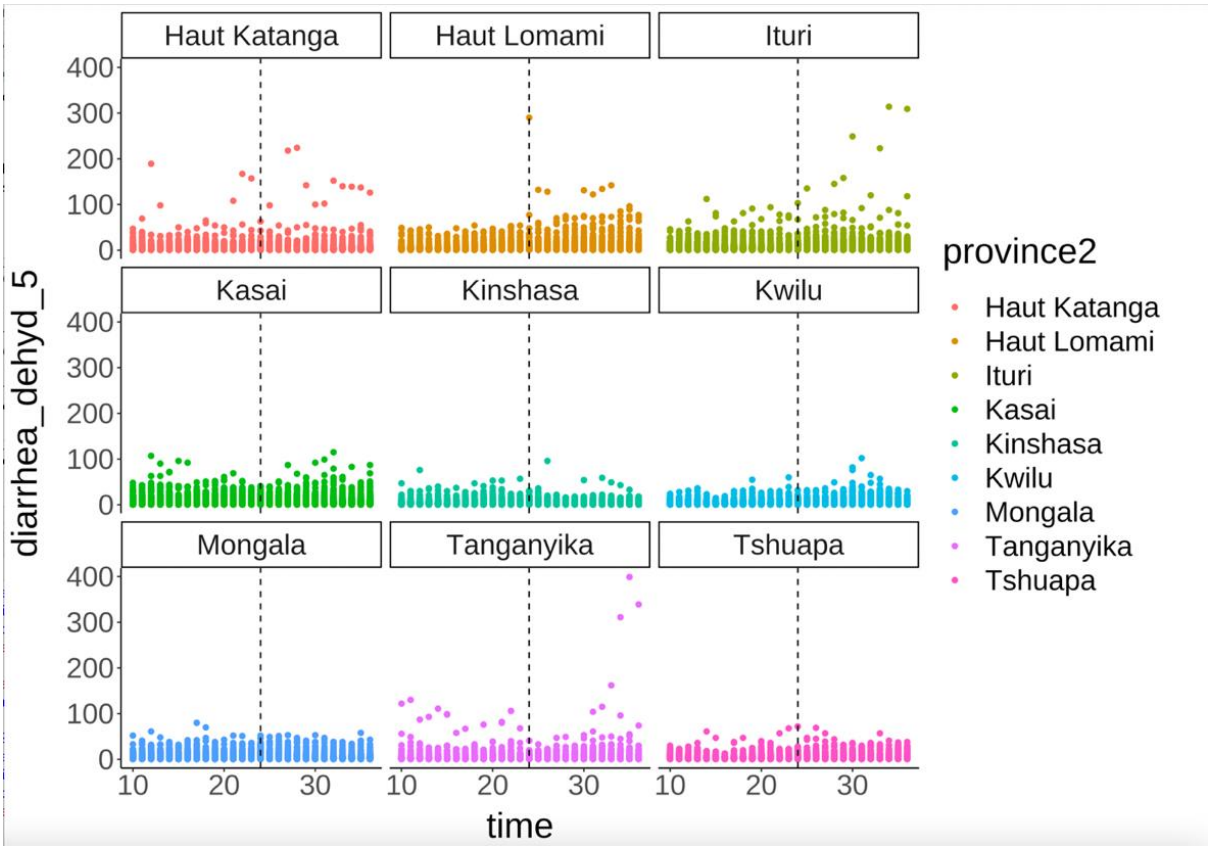


Figure 2b


Haut Katanga
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300
400
10
20
30
time
province2
Haut Katanga
Haut Lomami
Ituri
Kasai
Kinshasa
Kwilu
Mongala
Tanganyika
Tshuapa

Figure 3. Provincial Plots of dehydrated diarrheal disease cases over time: a. Plots of Severe Dehydrated Diarrheal Disease cases over time in Non-Mashako Provinces, b. Plots of Severe Dehydrated Diarrheal Disease cases over time in Mashako Provinces

Figure 3a

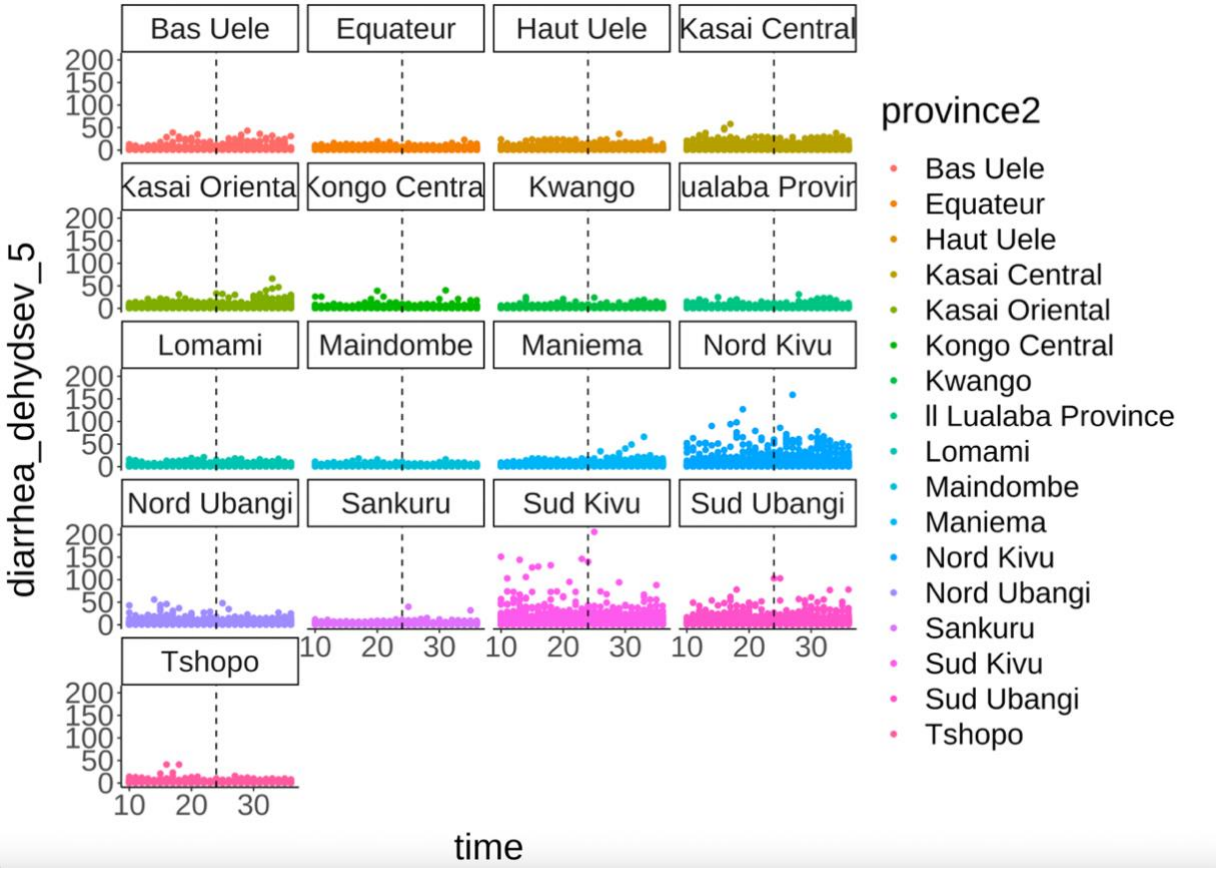

Figure 3b

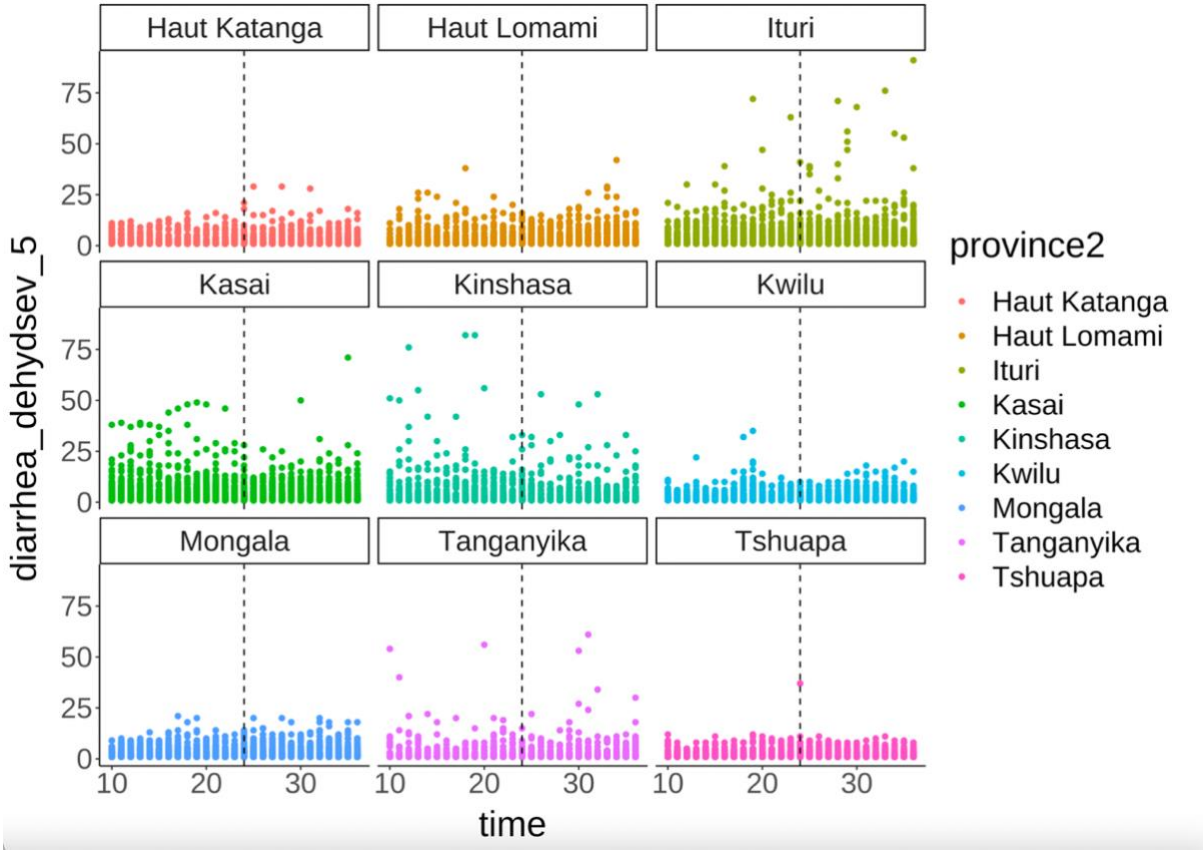
Haut Katanga
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Figure 4. Map from Recurrent Cholera Outbreaks, Democratic Republic of the Congo, 2008–2017[73]

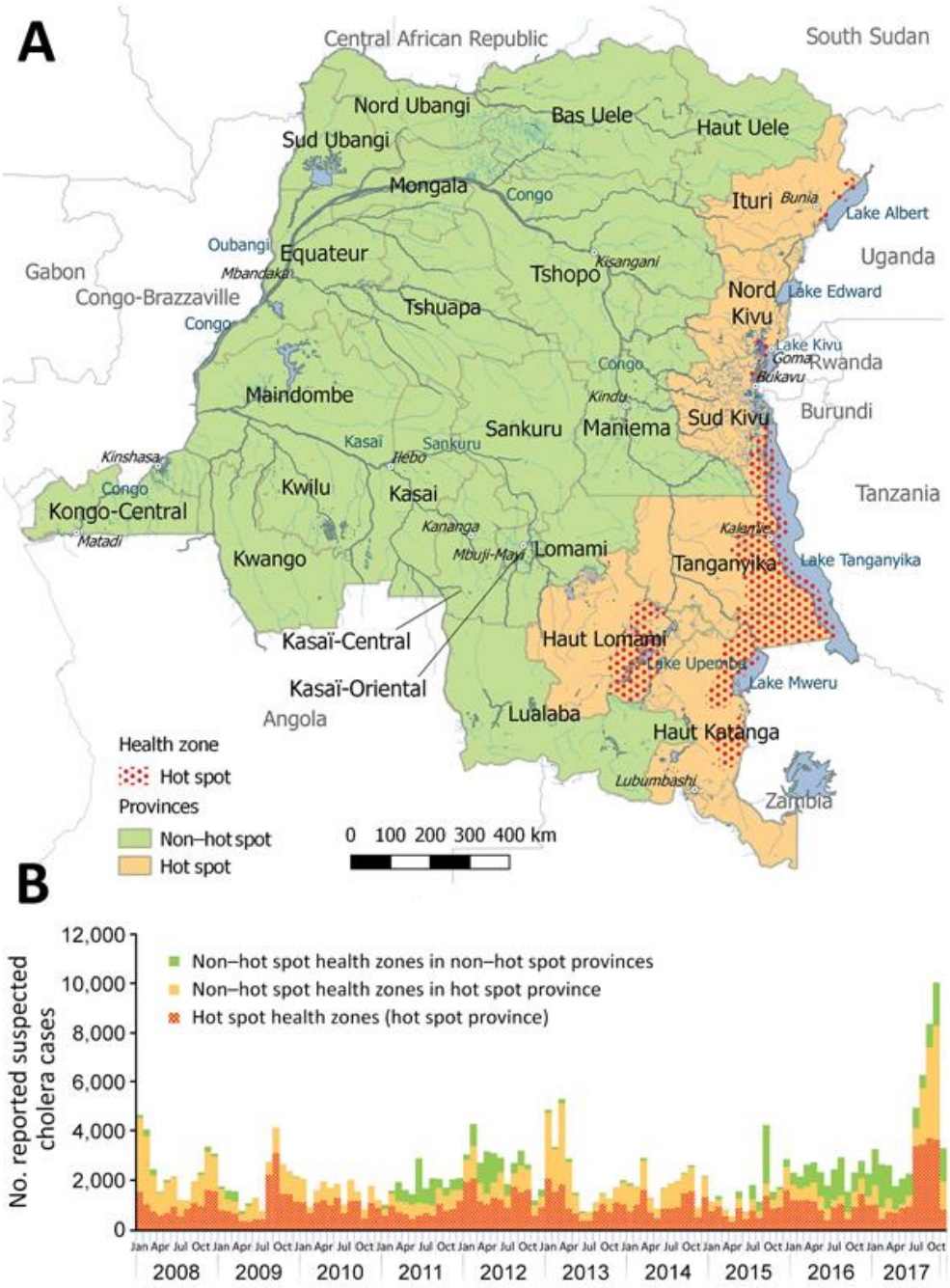
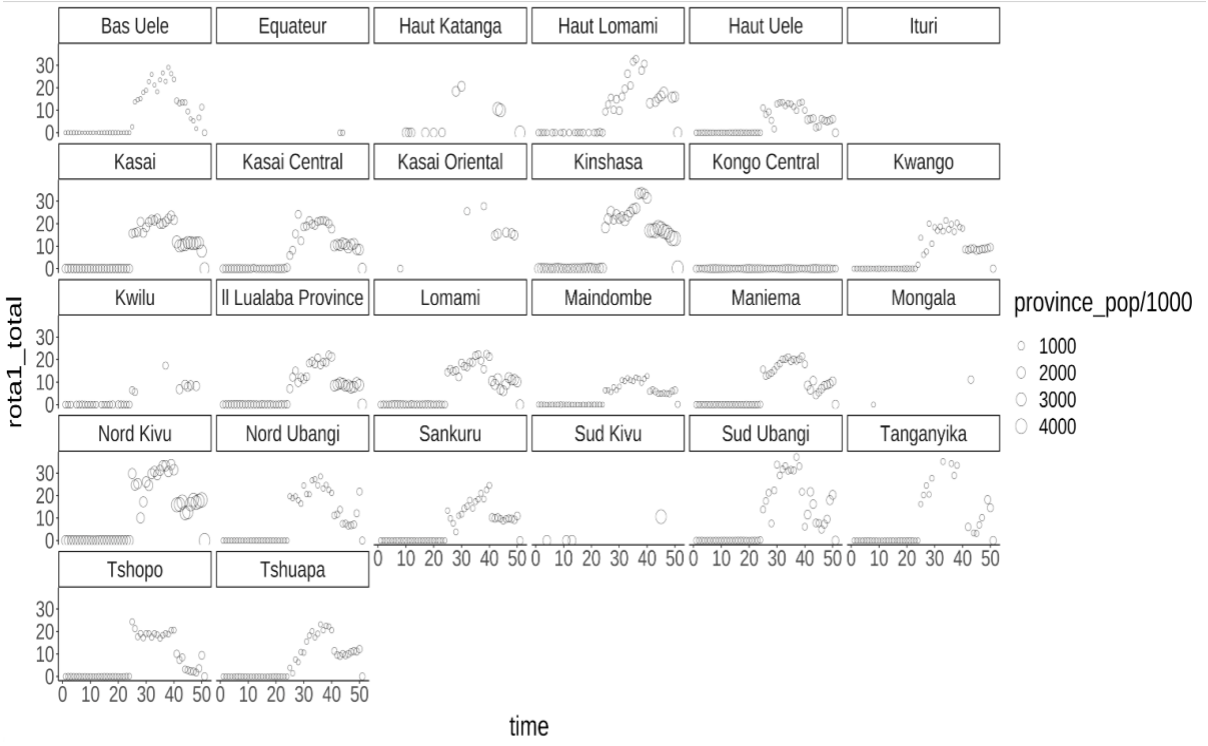


Figure 5. Rota Doses Administered



Chapter 5: Conclusion

5.1 MAIN RESULTS

The Democratic Republic of Congo (DRC) has historically struggled with low vaccination coverage, with full routine immunization (RI) coverage below 50% in 2013-2014 and 2017-2018[24,26]. To address this issue, the DRC EPI developed an emergency strategy to strengthen the RI system called the Mashako Plan in 2018, a multi-pronged policy aimed at revitalizing immunization services. The plan targeted key areas such as vaccine availability, equity in vaccination services, monitoring and evaluation, workforce development, and data quality and management. This dissertation examines the initial impacts of this emergency revitalization strategy to strengthen the RI system in DRC, the "Mashako Plan", using innovative methods and multiple data sources.

Aim 1 uses cross-sectional Expanded Programme for Immunization (EPI) mobile supervision surveys to assess process indicators for RI services and accessibility in DRC. The results suggest that the RI system is resilient to global trends, such as the COVID-19 pandemic, but sensitive to internal events, such as healthcare worker strikes. Aim 2 uses administrative data to evaluate the impact of the Mashako Plan on RI services in the initial nine provinces where it was implemented, using an interrupted time series analysis. The analyses show a positive trend in the percentage change of vaccine doses administered for penta3, penta1, and measles vaccines, indicating the success of the Mashako Plan in increasing vaccine doses administered through the RI system in DRC. Aim 3 evaluates the impact of the introduction of the rotavirus vaccine on diarrheal disease cases in children under 5 years in the DRC and does not see significant changes in the first year. While the results from this study were limited due to time and existing surveillance data limitations, the potential decrease in diarrheal cases warrants future research, particularly in light

of the limitations with available data that may mask decreases in diarrheal cases until more years of data is available. Aim 3 highlights the importance of documentation and surveillance when introducing new vaccines into the RI systems, both in general and in DRC.

Overall, the findings demonstrate the importance of implementing comprehensive policies to address low vaccination coverage in LMICs. The Mashako Plan, which took a cross-sectoral approach to revitalizing the RI system, was broadly successful in improving RI accessibility in DRC. However, continued monitoring and evaluation are necessary to assess regional variation and long-term impacts of such policies and identify areas for improvement.

5.2 STRENGTHS

The dissertation's strengths lie in the use of multiple data sources and methods that allow for causal inferences from population-based data. The DHIS2 data provide extensive information about the health system throughout the entire country, while the quasi-experimental methods used provide a deeper analysis than the descriptive statistics usually provided. The data from DHIS2 is particularly useful when there is limited time-series or survey data available because it is collected monthly and at the lowest administrative level. It provides valuable insight into the utilization side of the RI system. These results provide additional context and justification for partners and collaborators to support strategy and development around immunizations, including the support of the logistics of the RI system as well as new vaccine introduction. Additionally, the methods used are easily adaptable for future analyses by the Ministry of Health and EPI program to draw more causal inferences from the data they are already consistently collecting.

The EPI Mobile Supervision data is a unique resource that provides additional insight into the routine immunization system, especially the process indicators that allow the system to function.

These data can provide valuable insight into the resilience of the RI system and show trends in accessibility of RI services. When paired with the DHIS2 administrative data, these data sources provide a more complete picture of the routine immunization system as a whole and insight into the revitalization measures that successfully support that system.

5.3 LIMITATIONS

The biggest limitation of the data being used is that it is population-level data, and therefore no individual-level inferences may be made. DHIS2 suffers from the same issues as many other large data management systems, such as missing data, inaccurate data, and inconsistent or late reporting, which are the result of limited resources such as connectivity, functioning technology, well-trained and paid staff, and resources to conduct vaccination activities. The EPI Mobile Supervision data, although detailed, is limited because it is only collected at the health area level and is not consistent at the health facility level. Furthermore, the data being used in this study only covers a specific geographic area and may not be representative of other regions or countries. Even within DRC there is variation between provinces that warrant a deeper look at a sub-national level. Therefore, caution should be exercised when generalizing the findings to other settings. Finally, the study primarily focuses on routine immunization accessibility and does not consider other important factors that may influence vaccine uptake, such as demand generation. The initial Mashako Plan was design to address issues in accessibility, but future studies should evaluate the Mashako 2.0 indicators to get a more nuanced picture of the indicators that impact both accessibility and demand in the RI system.

5.4 CONCLUSIONn

In conclusion, this dissertation highlights the broad success of the Mashako Plan in improving routine immunization accessibility in the DRC through a comprehensive policy that targeted key

areas such as vaccine availability, equity in vaccination services, monitoring and evaluation, workforce development, and data quality and management. The use of multiple data sources and quasi-experimental methods allowed for deeper analysis and causal inferences from population-based data. These analyses demonstrate that administrative data can be valuable for program evaluation due to large amounts of data consistently collected at the lowest administrative levels and provide details about RI system utilization over time. This information along with RI system accessibility data from sources such as the EPI mobile supervision data, provide a clearer picture of how the entire RI system functions in DRC and may make it easier to identify areas for additional intervention. However, the limitations of the data sources, such as the accuracy of population estimates and missing or inconsistent data, highlight the need for continued monitoring and evaluation to identify additional areas for improvement.

Overall, this dissertation contributes to the growing body of evidence that comprehensive policies and cross-sectoral approaches are essential for addressing challenges to RI systems in low- and middle-income countries (LMICs). The findings underscore the importance of sub-national analyses, especially in a country as vast as DRC, in order to better tailor public health interventions to the unique needs of each region. The administrative and supervisory data utilized in this dissertation, while not commonly used for research, provide a wealth of knowledge that can be harnessed to more rigorously assess the impacts of new public health interventions. By leveraging these data sources with greater foresight and planning, it is possible to improve surveillance data to evaluate health interventions and new vaccine introductions more robustly. These results demonstrate the urgent need for DRC, and other countries, to invest in the expansion of their surveillance systems and development of effective planning strategies for new health intervention implementation. Further research is needed to evaluate the long-term sustainability of the Mashako

Plan's impact on routine immunization in the DRC and to identify new strategies for improving immunization coverage in other LMICs.

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