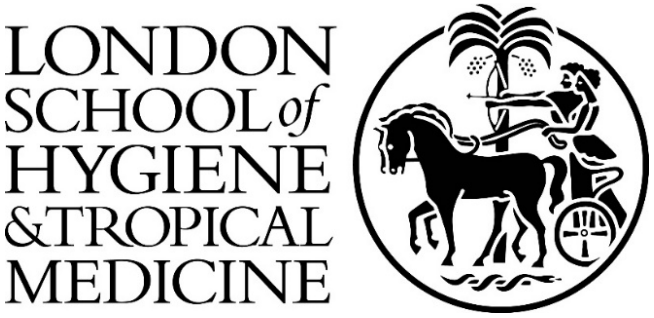


Timeliness of Routine Childhood Vaccination in The Gambia: Examining the Burden, Spatial Pattern, Determinants and the Impact of COVID-19 Pandemic

OGHENEBRUME WARIRI

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy (PhD)
of the
University of London

July 2024

Department of Infectious Disease Epidemiology

Faculty of Epidemiology and Population Health

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

The work contained in this thesis was funded by the EDCTP2 Programme, supported by the European and Developing Countries Clinical Trials Partnership, through a Career Development Fellowship awarded to Dr. Oghenebrume Wariri (grant number: TMA2019CDF-2734 – TIMELY)

Declaration

I, Oghenebrume Wariri, hereby declare that the work presented in this thesis is my original work and constitutes my own independent research. Where information has been derived from other sources, I have acknowledged and referenced them appropriately within the thesis.

Oghenebrume Wariri

Date: 30th July 2024

Supervisors and Advisory Committee

Supervisors

Assistant Professor Chris Grundy

Assistant Professor of Geospatial Information System

Department of Infectious Disease Epidemiology and International Health

Faculty of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

London, United Kingdom

Professor Beate Kampmann

Professor of Paediatric Infection and Immunity

Department of Clinical Research

Faculty of Infectious and Tropical Diseases

London School of Hygiene and Topical Medicine

London, United Kingdom

Professor Kris Murray

Professor of Environmental Change and Health

co-Director, Centre on Climate Change and Planetary Health

MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine

Fajara, The Gambia

Advisory Committee Members

Dr. Chigozie Edson Utazi

Lecturer

Southampton Statistical Sciences Research Institute and

WorldPop, School of Geography and Environmental Science

University of Southampton

Southampton, United Kingdom

Assistant Professor Uduak Okomo

Clinical Assistant Professor of Maternal & Newborn Health

Vaccines & Immunity Theme

MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine

Fajara, The Gambia

Abstract

The success of immunisation programmes is traditionally evaluated by measuring vaccination coverage rates, which assumes uptake, but overlooks if vaccine doses are delivered within the recommended and accepted timeframes. The timeliness of routine childhood vaccination shapes childhood vaccine-preventable diseases (VPDs) risk, thus, is an important public health metric. To achieve the goals of the Immunisation Agenda 2030, countries must also ensure that all children receive vaccination in a timely, age-appropriate manner.

While studies on the timeliness of childhood vaccination have gained traction in low-and middle-income countries (LMICs), many of them have key measurement and methodological gaps that limit their utility and comparability. These studies generated estimates of timeliness at the national or regional level, masking significant within and between country heterogeneities that hinders the identification of hotspots that could benefit from targeted interventions. Existing research have rarely explored the specific impact of supply-side determinants on vaccination timeliness, despite their known influence on the uptake of childhood vaccination. This PhD investigated the burden and spatial pattern of untimely childhood vaccinations in The Gambia, and examined the demand and supply-side determinants of timely vaccination. It also examined the impact of the COVID-19 pandemic on the timeliness of childhood vaccination in The Gambia.

The first objective of the PhD was to determine the methodological and measurement gaps in assessing vaccination timeliness in LMICs through a scoping review of existing literature. The review relied on the guidance framework for scoping reviews described by the *Joanna Briggs Institute*. The second objective leveraged the latest available nationally representative Demographic and Health Survey (DHS) data to investigate all dimensions of childhood vaccination timeliness, analysing outcomes across two birth cohorts in The Gambia. The second objective also identified the hotspots of untimely routine vaccination by leveraging a well validated fully Bayesian geostatistical modelling approach and generated high-resolution maps depicting the prevalence of untimely childhood vaccination in The Gambia. Additionally, this analysis identified specific districts with a combination of high estimated prevalence and a substantial number of affected infants.

The third objective of the PhD examined the impact of the COVID-19 pandemic on vaccination coverage and timeliness in The Gambia. This analysis leveraged a binomial interrupted time-series regression model and monthly longitudinal birth cohort data of 57,286 children in over 300 communities in two large Health and Demographic Surveillance Systems in The Gambia, covering five years preceding and two years during the COVID-19 pandemic. Finally, the fourth objective investigated the demand- and supply-side factors determining timely vaccination in The Gambia, guided by two complementary conceptual frameworks. To achieve this objective, two nationally-representative and temporally aligned datasets were integrated.

This PhD, through the most extensive review on the topic to date, spanning four decades and including 224 studies from 103 LMICs, identified significant measurement and methodological gaps in the existing literature on vaccination timeliness. Specifically, there was substantial variation in the definition, dimensions studied, and operationalisation of timeliness. The subsequent objectives of the PhD addressed these gaps through a robust approach. Delayed vaccination was the most common dimension of untimely vaccination in The Gambia, with the highest proportion and the longest median number of days children were vaccinated after the recommended time frames. The spatial modelling of vaccination timeliness, potentially the first globally, revealed significant subnational heterogeneity, with most 'hotspots' of delayed vaccination clustered in the eastern part of The Gambia. The COVID-19 pandemic had no significant negative impact on the timeliness and coverage of routine childhood vaccinations in The Gambia. Demand-side factors were the most common drivers of timely vaccination; however, supply-side factors such as travel time, availability of cold storage, and staffing levels at the nearest immunisation clinic were also significant determinants.

Taken together, the PhD research underscores the need for a comprehensive, nuanced and robust approach to measuring vaccination timeliness. The findings have key implications for policy and practice for The Gambian routine immunisation system and similar LMICs context. While optimising overall vaccination coverage rates and reaching zero-dose children remain crucial, focusing solely on these measures may obscure other important aspects of programme performance, particularly the timeliness of vaccination. This is even more important for ‘maturing’ immunisation systems like The Gambia, which, despite achieving relatively high routine vaccination coverage rates, continue to grapple with untimely vaccination and VPDs outbreaks.

Acknowledgements

I am deeply grateful to have had the invaluable guidance and support of my supervisors, Chris Grundy, Kris Murray, and Beate Kampmann, throughout this journey. Commencing my PhD amidst the challenges of the COVID-19 pandemic was daunting, but their unwavering support and mentorship steered me through the uncertainties. Their encouragement paved the way through the winding road of this PhD journey, smoothing out bumps along the path. I extend my heartfelt appreciation to Edson Utazi and Uduak Okomo for their insightful feedback and guidance as members of my advisory committee. The regular meetings, skill-building and feedback sessions were instrumental in shaping the final outcome of this endeavour.

My family has been my pillar of strength, providing unwavering support and encouragement when I needed it most. I extend my deepest gratitude to my beloved wife, Erhuvwu, and my children, Yoma and Wona, for their enduring belief in me and for standing by me throughout these three years. Erhuvwu, your steadfast companionship and love since the outset of my journey in medical school nearly two decades ago, through residency training, master's degree, and now my PhD, is beyond measure. Yoma and Wona, you made the whole process bearable. I always looked forward to coming home and goofing around with you both. It was fun discussing my research with you, even though you were only 13 and 9 when I completed the PhD. I hope I managed to be a good dad through it all. I also want to express my special thanks to my dad, Mereh Wariri, and my mom, Patricia Wariri, for instilling in me the drive for academic scholarship and the belief that moral uprightness trumps everything else. My sincere appreciation to my elder brother, Cephalus, who continues to be a great example for me and sparked in me the drive for academic excellence. Growing up, I always looked up to him. To my younger siblings; Tevwo, Oghenero, Onos, Ena, Ejiro, and Faith, you make me live everyday wanting to succeed in everything I do.

The WorldPop Project at the University of Southampton, led by Andy Tatem, along with the assistance of Edson and Winfred, provided invaluable support from the inception of my journey, guiding me and holding my hands through the intricacies of coding in R, spatial modelling, and mapping, to offering invaluable advice on geographic accessibility modelling. I also cherish the memories of my first night in Southampton when I came visiting and the welcoming buffet.

I extend my gratitude to The Gambia Expanded Programme on Immunisation, under the capable leadership of Mr. Sidat Fofana, for their unwavering support throughout the project. Special thanks to Malick and Alieu for their kind assistance. I am also thankful to the Health and Demographic Surveillance System Team at the MRC Unit The Gambia, especially Esu, for their invaluable support. This PhD research, which relied on multiple data sources, would not have been feasible without the capable assistance and support from the Data Management Core at the MRC Unit The Gambia, particularly Bai-Lamin and Lamin Saidy.

The Nigerian community at the MRC Unit The Gambia filled my journey with vibrant Naija vibes, and I am deeply grateful for their camaraderie. The "Elders" – Egere, Okebe, Uduak, and Bukky (my first line manager) – offered invaluable career guidance upon my arrival at the MRC Unit. My heartfelt appreciation also goes to Bola and Solomon, who became like elder brothers to me within the Nigerian community. To my friends and fellow travellers, Imam and Esin, thank you for fostering a healthy yet unspoken competition that has driven us all to excel in our careers.

The European and Developing Countries Clinical Trials Partnership (EDCTP) generously funded this project and the PhD through a Career Development Fellowship, and I am immensely grateful for their support and investment in my research idea. None of this would have been possible without the unwavering support and guidance of my mentor, Beate, who believed in me from the moment I arrived at the MRC Unit The Gambia. Beate, you have opened doors, advocated for me in rooms I couldn't enter, and provided invaluable advice when I needed it most. Your support has been truly instrumental, and for that, I am eternally grateful.

List of Publications

Below is a list of research articles that were published from my PhD research work.

1) **Wariri O,** Okomo U, Kwarshak YK, Murray KA, Grundy C, Kampmann B. Timeliness of routine childhood vaccination in low-and middle-income countries, 1978–2021: Protocol for a scoping review to map methodologic gaps and determinants. PLoS ONE. 2021 Jun 17;16(6):e0253423.

2) **Wariri O,** Okomo U, Kwarshak YK, Utazi CE, Murray K, Grundy C, Kampmann B. Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps. PLOS Global Public Health. 2022 Jul 14;2(7):e0000325.

3) **Wariri O,** Utazi CE, Okomo U, Sogur M, Murray KA, Grundy C, Fofanna S, Kampmann B. Timeliness of routine childhood vaccination among 12–35 months old children in The Gambia: Analysis of national immunisation survey data, 2019–2020. PLoS ONE. 2023 Jul 21;18(7):e0288741.

4) **Wariri O,** Utazi CE, Okomo U, Metcalf CJ, Sogur M, Fofana S, Murray KA, Grundy C, Kampmann B. Mapping the timeliness of routine childhood vaccination in the Gambia: a spatial modelling study. Vaccine. 2023 Sep 7;41(39):5696-705.

5) **Wariri O**, Utazi CE, Okomo U, Sowe A, Sogur M, Fofanna S, Ezeani E, Saidy L, Sarwar G, Dondeh BL, Murray KA, Grundy C, Kampmann B. Impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in the Gambia, 2015–2021. BMJ Global Health. 2023 Dec 1;8(12):e014225.

6) **Wariri O,** Utazi CE, Okomo U, Dotse-Gborgbortsi W, Sowe A, Sogur M, Fofanna S, Murray KA, Grundy C, Kampmann B. Multi-level determinants of timely routine childhood vaccinations in The Gambia: findings from a nationwide analysis. Status: Submitted Manuscript, Under Review. https://dx.doi.org/10.2139/ssrn.4742793 (Preprint)

Table of Contents

List of Figures and Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Paper 1

Paper 2

Chapter 5

Chapter 6

Chapter 7

Table of Abbreviations

AUC	Area Under the Curve
BCG	Bacille Calmette Guerin Vaccine
CI	Confidence Interval or Credible Interval
COVID-19	Coronavirus Disease (SARS-CoV-2)
DHS	Demographic and Health Survey
DTP	Diphtheria, Tetanus and Pertussis Vaccine
EDCTP	European and Developing Countries Clinical Trial Partnerships
EPI	Expanded Programme for Immunisation
GBoS	Gambian Bureau of Statistics
GDHS	The Gambian Demographic and Health Survey
GVIF	Generalized Variance Inflation Factor
HBR	Home-Based Records
HBV	Hepatitis B Virus
HDSS	Health and Demographic Surveillance System
HepB0	Birth dose of Hepatitis B vaccine
INLA	Integrated Nested Laplace Approximation
IQR	Interquartile Range
K43	NIH Emerging Global Leader Award
LGA	Local Government Area
LMIC	Low-and Middle-Income Country
MCV1	First-dose of Measles-Containing Vaccine
MICS	Multiple Indicator Cluster Survey
NIH	National Institutes of Health
OPV1	First dose of Oral Polio Vaccine
OPV2	Second dose of Oral Polio Vaccine
OPV3	Third dose of Oral Polio Vaccine
PCV1	First dose of Pneumococcal Conjugate Vaccine
PCV2	Second dose of Pneumococcal Conjugate Vaccine
PCV3	Third dose of Pneumococcal Conjugate Vaccine
PENTA1	First dose of Pentavalent Vaccine (combined DTwP-HepB-Hib vaccine)
PENTA2	Second dose of Pentavalent Vaccine (combined DTwP-HepB-Hib vaccine)
PENTA3	Third dose of Pentavalent Vaccine (combined DTwP-HepB-Hib vaccine)
PRISMA-ScR	PRISMA extension for Scoping Reviews
ROC	Receiver Operating Characteristic
ROI	Return on Investment
VIF	Variance Inflation Factor
VPC	Variance Partition Coefficient
VPD	Vaccine Preventable Disease
WHO	World Health Organization

List of Contributors

I, Oghenebrume Wariri, designed the objectives of my PhD studies and took lead responsibility for the quality of the data utilised throughout this thesis. This included data curation, cleaning, integration, and validation. I also performed all analyses and wrote all sections of the thesis, including the manuscripts, incorporating valuable input from my supervisors and PhD advisory committee members.

While I collaborated with The Gambia Immunisation programme to update the Immunisation Facility Mapping and Census dataset with additional variables, the field work for data collection in the nationally-representative Demographic and Health Survey (DHS), the Farafenni and Basse Health and Demographic Surveillance System (HDSS), and the National Immunisation Facility Mapping and Census in The Gambia was primarily conducted by the institutions that commissioned and oversee these data platforms. Specific contributions of others to the work in this thesis are listed below.

Name	Position and Institution	Contribution
Chris Grundy	Assistant Professor of Geospatial Information System, Department of Infectious Disease Epidemiology and International Health, London School of Hygiene and Tropical Medicine, UK.	PhD Supervisor
Beate Kampmann	Professor of Paediatric Infection and Immunity, Department of Clinical Research, London School of Hygiene and Tropical Medicine, UK.	PhD Supervisor
Kris Murray	Professor of Environmental Change and Health, Centre on Climate Change and Planetary Health, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	PhD Supervisor
Chigozie Edson Utazi	Lecturer, Southampton Statistical Sciences Research Institute (SSSRI) and WorldPop, School of Geography and Environmental Science, University of Southampton, UK.	PhD Advisor. Provided guidance and advise on the statistical methods and spatial modelling approach.
Uduak Okomo	Clinical Assistant Professor of Maternal & Newborn Health, Vaccines & Immunity Theme, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	PhD Advisor. Provided guidance on the scoping review methodology, The Gambian health system and immunisation programme.
Winfred Dotse-Gborgbortsi	Research Fellow, WorldPop, School of Geography and Environmental Science, University of Southampton, UK.	Collaborator. Provided guidance on modelling geographic accessibility, working with DHS data and coding in R.
Sidat Fofana	Programme Manager, The Expanded Programme on Immunisation (EPI),	Collaborator. Provided access to National Immunisation

	Department of Health Services, Ministry of Health, The Gambia.	Facility Mapping and Census data and expert knowledge on contextual information about The Gambian immunisation system.
Alieu Sowe	Data Manager, The Expanded Programme on Immunisation (EPI), Department of Health Services, Ministry of Health, The Gambia.	Collaborator. Provided expert knowledge on contextual information about The Gambian immunisation system.
Malick Sogur	Cold-Chain and Logistic Officer, The Expanded Programme on Immunisation (EPI), Department of Health Services, Ministry of Health, The Gambia.	Collaborator. Provided expert knowledge on contextual information about The Gambian immunisation system.
Coite Manuel	founder and CEO, Crosscut, Washington DC, USA.	Access to National Immunisation Facility Mapping and Census data, provided additional information about the facility geolocation and mapping process.
Esu Ezeani	Head of Health and Demographic Surveillance System (HDSS), MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	Access to Farafenni and Basse HDSS data, 2015 – 2021.
Lamin Saidy	Junior Data Manager, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	Designed database, coordinated the extraction of HDSS data, data entry and management.
Yakubu Kevin Kwarshak	Senior Registrar, Department of Surgery, Jos University Teaching Hospital (JUTH), Jos, Nigeria.	Screened titles and abstracts, reviewed full texts of relevant articles, and extracted data during scoping review.
Njilan Johnson	Programme Manager, Vaccines and Immunity Theme, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	Project Logistics and budgetary support.
Awa Badjan and Jebel Ceesay	Project Officers, Research Support Office (RSO), MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	Project Logistics.
Stefan Flasche	Professor of Vaccine Epidemiology, Department of Infectious Disease Epidemiology and Dynamics, London School of Hygiene and Tropical Medicine, UK.	PhD Upgrading Examiner
Alison Elliott	Professor of Tropical Medicine, Clinical Research Department, London School of Hygiene and Tropical Medicine (LSHTM), and MRC/UVRI & LSHTM Uganda Research Unit, Uganda	PhD Upgrading Examiner

Thesis outline

This PhD thesis is divided into three parts and consists of seven chapters presented in the ***research paper style***. Part 1, which includes Chapters 1 and 2 provides the background and objectives of the research. Part 2, which comprises Chapters 3, 4, 5 and 6, consist of analytical chapters, which are presented as research papers. Finally, Part 3, which is Chapter 7 presents a general discussion, future direction for research, recommendations and the conclusion of the PhD research. An overview of the outline is provided below.

PART 1: BACKGROUND AND OBJECTIVES

Chapter 1 sets the stage by exploring the critical role of childhood immunisation and the key indicators used to track progress in vaccination programmes. It introduces the concept of vaccination timeliness, highlighting its significance as a marker of programme quality. Additionally, the chapter provides a comprehensive overview of The Gambia's routine immunisation programme, including the specific vaccines offered, their recommended schedule, and the programme's achievements and challenges. Finally, it critically evaluates past research on vaccination timeliness in The Gambia, identifying limitations and paving the way for the scientific rationale behind the PhD research.

Chapter 2 of the thesis provides an overview of the aim, hypothesis, and objectives of the PhD research. It also presents an overview of the different methodologies used throughout the research. There is no overall methods section because the methods used to address each of the PhD objective differ. Detailed methods to achieve each objective are thus presented in the respective chapters, within the included research papers and the accompanying supplementary materials.

PART 2: ANALYTICAL CHAPTERS

Chapter 3 of this thesis addresses the first objective of my PhD, which was to systematically review the literature to understand the measurement and methodological gaps in the existing research on vaccination timeliness in low-and middle-income countries. The insights gained from this scoping review of the literature played a crucial role in shaping the design of my subsequent PhD studies. This chapter is presented as two published research papers; Research Paper 1 (appendix): **Wariri O,** Okomo U, Kwarshak YK, et al. Timeliness of routine childhood vaccination in low-and middle-income countries, 1978–2021: Protocol for a scoping review to map methodologic gaps and determinants. PLoS ONE. 2021. Research Paper 2: **Wariri O,** Okomo U, Kwarshak YK, et al. Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps. PLOS Global Public Health. 2022

Chapter 4 of the thesis addresses the second objective of my PhD, which was to examine the burden and spatial pattern of the timeliness of routine childhood vaccination in The Gambia. This chapter is presented as two published research papers. Research Paper 3: **Wariri O,** Utazi CE, Okomo U, et al. Timeliness of routine childhood vaccination among 12–35 months old children in The Gambia: Analysis of national immunisation survey data, 2019–2020. PLoS ONE. 2023. Research Paper 4: **Wariri O,** Utazi CE, Okomo U, et al. Mapping the timeliness of routine childhood vaccination in the Gambia: a spatial modelling study. Vaccine. 2023.

Chapter 5 addresses the third objective of my PhD which was to examine the impact of COVID-19 pandemic on the timeliness of routine childhood vaccination in The Gambia. This chapter includes one published research paper. Research Paper 5: **Wariri O**, Utazi CE, Okomo U, et al. Impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in the Gambia, 2015–2021. BMJ Global Health. 2023.

Chapter 6 of the thesis focuses on the fourth and final objective of my PhD research, which was to investigate the multi-level determinants (demand and supply-side) of timely routine childhood vaccinations in The Gambia. This chapter is presented as a research paper that has been submitted for peer-review and is currently undergoing review. Research paper 6: **Wariri O,** Utazi CE, Okomo U, et al. Multi-level determinants of timely routine childhood vaccinations in The Gambia: findings from a nationwide analysis. Status: Submitted Manuscript Under Review.

PART 3: GENERAL DISCUSSION, CONTRIBUTION OF THE PHD TO LITERATURE AND DIRECTION FOR FUTURE RESEARCH

Chapter 7 of the thesis summarises the main findings from the four analytical chapters and discusses their interconnectedness, highlights the conceptual and methodological contributions to the literature, as well as its limitations. Additionally, this chapter highlights the implications of the PhD research for programme and policy and presents direction for future research. Finally, the chapter ends with key recommendations and concluding remarks.

PART 1: BACKGROUND AND OBJECTIVES

Chapter 1: Introduction

1.1 Global status of routine childhood immunisation

The global Expanded Programme on Immunisation (EPI), launched by the World Health Organization (WHO) during the 27th World Health Assembly in May, 1974,[1] has seen remarkable success. The catalyst for the launch of the EPI was the substantial progress made towards global smallpox eradication in the 1970s, a milestone that was achieved in 1978 due to smallpox vaccination.[1] At its outset, the WHO aimed to vaccinate all children against smallpox, tuberculosis, diphtheria, tetanus, pertussis, poliomyelitis, and measles through the EPI by 1990.[2] Due to its success, EPI currently provide protection against other global and regional specific pathogens, across the life course.[3] The inclusion of new vaccines into the EPI schedule, and the specific ages or timeframes for their administration, is typically driven by local or region-specific epidemiological situations and country programme decisions.[1]

The EPI has significantly reduced the incidence and mortality from childhood vaccine-preventable diseases (VPDs). A prime example is polio, a crippling childhood disease that was once a global threat. Thanks to widespread routine childhood vaccination, polio is now on the verge of eradication, like smallpox which was eradicated more than four decades ago.[4] In 2022, only 22 cases of wild poliovirus type 1 were reported in Afghanistan and Pakistan compared with 1988 when wild poliovirus paralysed over 350 000 children across 125 countries.[5] But the benefits extend beyond polio or smallpox. The EPI is the single greatest contributor to global child survival, having averted 154 million deaths since its inception in 1974.[3] In low- and middle-income countries (LMICs) alone, vaccination programmes have saved the lives of 36 million children under-5 between 2000 and 2019.[6] Vaccines are not just about protecting people; they are a powerful public health tool with exceptional cost-effectiveness. Studies show that for every dollar invested in immunisation programmes, there's a return on investment of over 16 dollars.[7] This number jumps to 48 dollars when the wider benefits, like reduced healthcare costs and increased productivity are considered.

Despite significant progress in reducing morbidity and mortality from VPDs, and the clear economic benefits of routine immunisation programmes, major challenges persist in many countries.[8] Unfortunately, the benefits of vaccination are not distributed equally. Coverage varies significantly within and between countries, with some subpopulations facing the greatest barriers. These subpopulations often include the poorest, most marginalised, and vulnerable people, particularly in fragile and conflict-affected settings.[9] An alarming 20 million children miss out on completing even basic vaccinations each year, with an even higher number missing newer vaccines.[9] Notably, almost half of these unvaccinated children reside in the WHO African Region. Furthermore, in 2022, over 14.3 million received no vaccines at all through routine programs, known as "zero-dose"

children (Figure 1).[10] In some countries, progress has plateaued since 2009 or even declined (Figure 1), raising concerns that complacency could jeopardize past achievements.

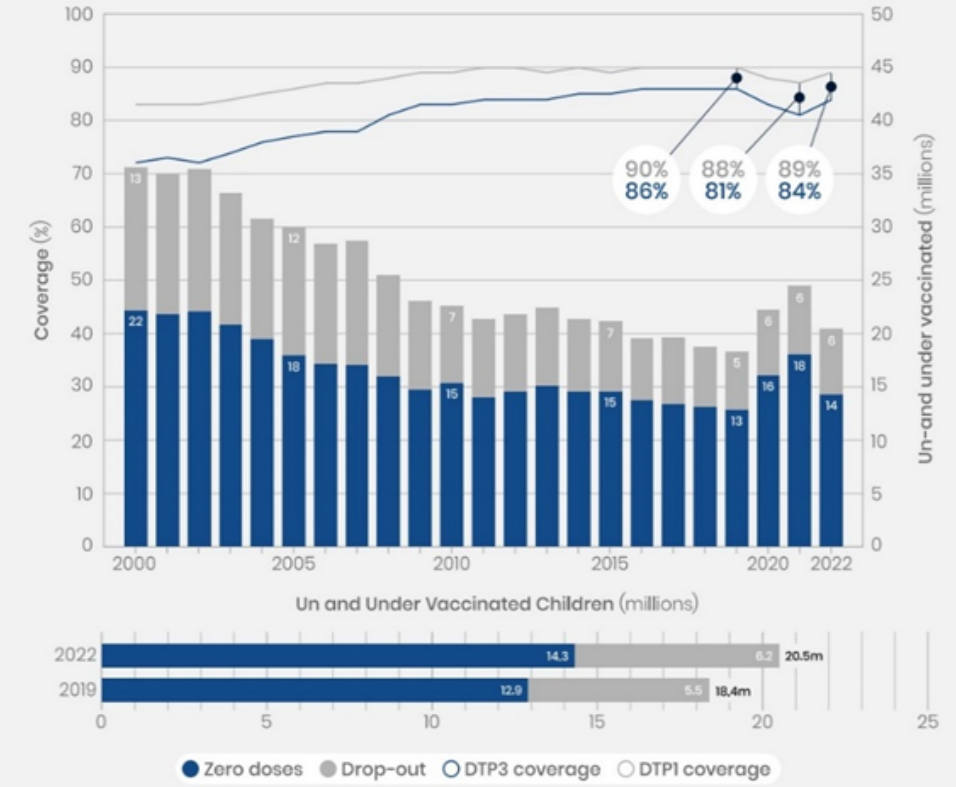


Figure 1: Global trends in estimated vaccine coverage and zero-dose children, 2000 – 2022.
Image source: World Health Organization, 2023.[10]

The recent global resurgence of measles serves as a stark reminder of how hard-won gains of routine immunisations can easily be eroded. Measles is a highly transmissible VPD and its occurrence acts as a "canary in the coalmine", quickly exposing any immunity gaps in the population.[10] In 2018, over 140,000 people died due to measles globally - a tragic figure that highlights the urgent need for action.[11] While the reasons for these outbreaks varied within and between countries, low coverage of the first dose of the measles-containing vaccine (MCV1), declining confidence in vaccines, and previously unidentified immunity gaps were important contributing factors.[12] Even in Europe, where more children were vaccinated against measles than ever before, over 80,000 people across 47 of 53 countries contracted measles in 2018, resulting in 72 deaths – the highest number in a decade.[13] The worst impacts were felt in sub-Saharan Africa, where many children consistently miss out on vaccination.[11] The Democratic Republic of the Congo, Liberia, Madagascar, and Somalia were the most affected countries, accounting for nearly half of all global measles cases in 2018.[11]

Earlier in 2010, the WHO launched the Global Vaccine Action Plan (GVAP) for the decade 2011–2020, with the aim of ensuring that all countries worldwide achieve a coverage of 90% for all childhood vaccines by 2020, among other targets.[14] However, only 11 countries/territories had met

the GVAP target of reaching and maintaining 90% coverage across the assessed vaccines in 2019.[15] Recognising the role of childhood vaccination in global health security and the cost-effectiveness of vaccination, the Immunisation Agenda 2030 (IA2030) was officially launched in 2021 as a comprehensive and inclusive framework for the decade 2021–2030. The IA2030 is more ambitious than GVAP, striving for a 50% reduction in the number of zero-dose children, the introduction of 500 new vaccines in LMICs by 2030, and ultimately achieving "a world where every-one, everywhere, at every age fully benefits from vaccines".[9] Central to its core strategies, the IA2030 seeks to prioritise the subpopulations that are usually not reached by lifesaving vaccines or are under-immunised. However, the COVID-19 pandemic presents a significant challenge, jeopardising these crucial objectives.

The global COVID-19 pandemic overstretched health systems. It amplified the already existing gaps which prevented countries from reaching global immunisation targets.[16] In 2020, an estimated 23 million children aged 12 months or younger did not receive their basic vaccines, which is 3.7 million more children than in 2019.[17] 60% of these children disproportionately lived in 10 LMICs. Estimates also suggest that the COVID-19 pandemic prevented 8.9 million children from receiving their routine MCV1 vaccination in 2020.[18] This setback reversed years of progress, and 39 of the 68 Gavi-supported vaccine introductions slated for 2020 were delayed due to COVID-19.[19] Although there is some evidence of recovery, a pulse survey conducted in late 2021 found that over half of the 129 participating countries reported continued disruptions in routine immunisation.[20] Furthermore, a multi-country analysis of the African continent in 2020 found that 13 of 15 included countries demonstrated evidence of declines in the monthly number of vaccine doses delivered across several antigens.[21] It is worth noting that Guinea and Liberia experienced similar disruptions to routine vaccination during their 2013-2015 Ebola outbreaks, later followed by measles resurgence.[22,23] While the latest WHO and UNICEF Estimates of National Immunisation Coverage (WUENIC) show a decrease in "zero-dose" children compared to 2021, pre-pandemic levels have not been achieved (Figure 2).[10]

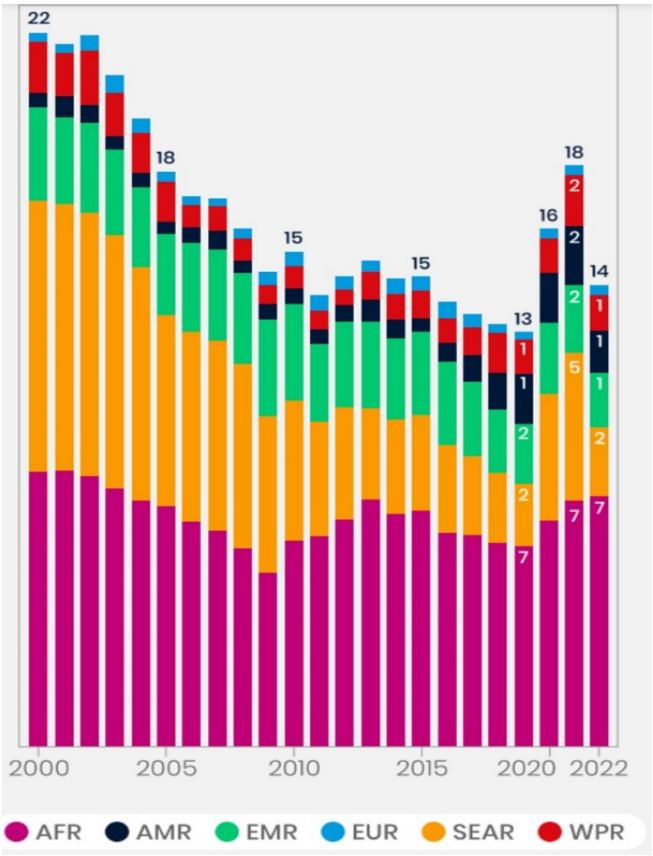


Figure 2: Zero-dose children (in millions) by WHO regions. Note: AFR = African Regions; AMR = American Region; EMR = Eastern Mediterranean Region; EUR = European Region; SEAR = South East Asian Region; WPR = Western Pacific Region.
Image source: World Health Organization, 2023.[10]

1.2 Monitoring the performance of routine immunisation systems

Routine immunisation programmes have a significant impact on reducing childhood morbidity and mortality from VPDs. Therefore, monitoring the performance of immunisation programmes is crucial in assessing the health system's overall performance. To achieve this, the immunisation system is generally divided into five key components (Figure 3),[24] with each component further divided into key indicators for evaluation.[a] The commonest indicators for evaluating and monitoring the performance of immunisation programmes include: vaccination coverage; up-to-date vaccination; zero-dose children; new vaccine introductions; drop-out rate, equity of vaccination coverage, and incomplete vaccination.[25] These indicators are part of the 'Service Delivery' component of the immunisation system.

Vaccination coverage is the traditional and most common indicator for evaluating and monitoring the performance of immunisation programmes. It refers to the proportion of the target population vaccinated with a specific vaccine dose by any date before data collection.[24,26] This indicator, which belongs to the service delivery component of the immunisation system, provides information on how effectively the immunisation programme is reaching its target population (Figure 3).[24] Vaccination coverage is also a primary proxy indicator for monitoring progress towards various vaccine-specific global health strategies, including the GVAP, IA2030, Reach Every District (RED) strategy, and the Measles and Rubella Strategic Framework 2021-2030. For instance, these four strategies aim to achieve a national vaccination coverage of 90%,[14] coverage of 90% for essential vaccines,[9] 80% vaccination coverage in all districts,[27] and at least 95% vaccination coverage with two doses of measles and rubella-containing vaccines in each district of every country,[28] respectively. Moreover, coverage also serves as an indicator for monitoring progress towards the Sustainable Development Goals and was also part of the Millennium Development Goals.

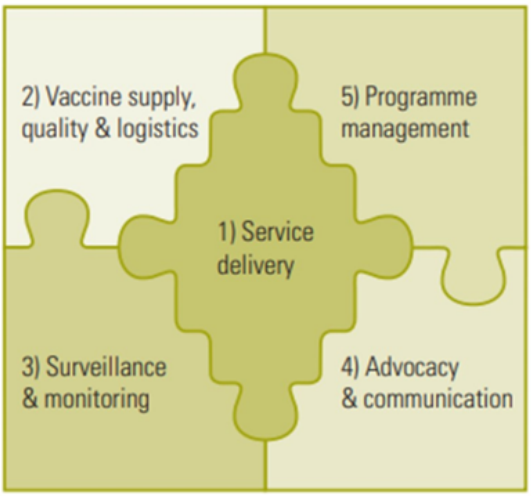


Figure 3: Five components of the immunisation system. **Image source:** World Health Organization, 2008.[24]

[a] **Service Delivery** include vaccination coverage, drop-out rates and existence of national plan for immunisation. **Vaccine Supply, Quality and Logistics** include availability of operational cold-chain equipment, availability of vaccine stocks and continuity of services, implementation of multi-dose vial policy, etc. **Surveillance and Monitoring** include completeness and timeliness of reporting, outbreak investigation initiated within 48 hours, proportion of VPDs confirmed by laboratory etc. **Advocacy and Communication** include availability of social mobilization or overall communication plan, availability of specific strategy for hard-to-reach population, etc. **Programme Management** include government funding for vaccines and programme operations, multiple-year commitment to financing, proportion of planned supportive supervision conducted, existence of micro-plans for each district, adequacy of personnel training, etc.

While vaccination coverage is an important measure of how effective an immunisation programme is in reaching its intended population, it does not provide the whole picture. The concept of "*zero-dose*" children has emerged as a crucial indicator for monitoring the performance of immunisation systems. For operational purposes, zero-dose children are defined as those who have not received the first dose of the Diphtheria, Tetanus, and Pertussis containing vaccine (DTP1).[29] This indicator is a key priority for both Gavi's 5.0 Strategy[30] and the IA2030,[9] which aims to reduce the number of zero-dose children by 50% globally by 2030. However, the IA2030 goes beyond coverage and zero-dose children. It also emphasises the *number of new vaccines* successfully introduced as a key service delivery indicator for monitoring the performance of immunisation systems.[9] Another important indicator for monitoring immunisation system performance is the *drop-out rate* between two vaccine doses (e.g., the drop-out rate between DTP1 and DTP3).[24,26] It is calculated by comparing the number of children who started receiving vaccination to the number that received subsequent vaccine doses.[24,26] Drop-out rate reflects the percentage of children who start a vaccination schedule but do not complete it. This indicator can be useful for defaulter tracking mechanisms.

Achieving equity in immunisation systems is crucial to the Gavi's 5.0 Strategy of "Leaving no-one behind with immunisation",[30] and aligns with the "Everyone, Everywhere" vision of the IA2030 agenda.[9] Therefore, *equity in vaccination coverage* based on location, sex, age, social or cultural background, is another crucial indicator of immunisation system performance.[9] This indicator is measured by comparing the vaccination coverage in one subpopulation to another, such as children from the poorest households compared to those from the richest or those in urban areas compared to those in rural settings.[31] To identify location-based or geographic inequalities in vaccination coverage, it is crucial to have spatially detailed data that goes beyond national or regional averages. This type of data helps to pinpoint areas with low or inadequate vaccination coverage and determine the best strategies to bridge the gap and improve overall coverage. Geospatial modelling approaches that use geolocated household survey data have become an important tool for generating high-resolution estimates and maps of vaccination coverage, and have gained prominence in recent years.[32,33] This type of equity-based, spatially detailed, vaccination coverage indicator is highly relevant for immunisation programmes, as recognised by global health policy frameworks such as the WHO IA2030 and Gavi Strategy 5.0,[9,30] which aims to achieve equity in vaccination coverage.

1.3 Timeliness of routine childhood vaccination

The traditional measure of immunisation programme performance, vaccination coverage, has certain limitations that make it an imperfect indicator of the effectiveness of vaccination programmes.[34] Conceptually, vaccination coverage assumes uptake, and overlooks whether doses were received within the recommended age window. Vaccination coverage does not account for

whether doses were administered too early, late or improperly spaced,[35] rather, it classifies children into two groups: those who are vaccinated and those who are not. This approach oversimplifies the reality, concealing a spectrum of situations within each group that can affect vaccine effectiveness and protection from VPDs. Seemingly high-coverage populations may exhibit poor performance if the timing and adherence to recommended vaccination schedules are taken into account. A study in Malawi confirms this, where 93% of children had received DTP3 by the age of 23 months, but only 2% had received it at the recommended age of 14 weeks.[36] Another study found that only 18% of children in the United States received all their vaccinations at the recommended times, despite vaccination coverage rates reaching record-high levels.[37] This shows that vaccination coverage can overestimate protection and mask significant immunity gaps arising from non-adherence to recommended vaccination schedules. Therefore, while coverage remains an important indicator, it is crucial to consider additional quality indicators, such as timeliness of vaccination, to fully assess programme effectiveness.[38,39]

Timeliness of vaccination – i.e., vaccines received within the recommended vaccination schedule, in an age-appropriate manner, is a measure of effective vaccination coverage.[25] The purpose of the vaccination schedule is to protect children during their first year of life, when they are most vulnerable.[40] Determining the optimal timing for vaccination depends on several factors, such as the epidemiology of VPDs, waning of maternal antibodies, and identifying the earliest safe age for vaccination with optimal efficacy and minimal risks.[41] Other factors that determine the optimal timing of vaccination include the age at which the child is at the greatest risk of VPDs and when their immune system is mature enough to provide maximum response to the vaccine (Figure 4).[42] The US measles epidemic of 1989-1990 was attributed to a failure to provide timely vaccination to children at their most vulnerable period, according to the recommended schedule.[43] This resulted in many children being exposed to measles for longer than they should have been. Pertussis is a another example of the significance of timely vaccination. Since siblings can transmit pertussis to infants who are too young to be vaccinated, vaccinating these children according to the recommended schedule can indirectly protect their younger siblings by minimising their exposure.[44,45] These examples highlights the need for high coverage and timely vaccination, i.e., ensuring that a high proportion of children receive their doses at the optimal and recommended time for maximum protection.[25]

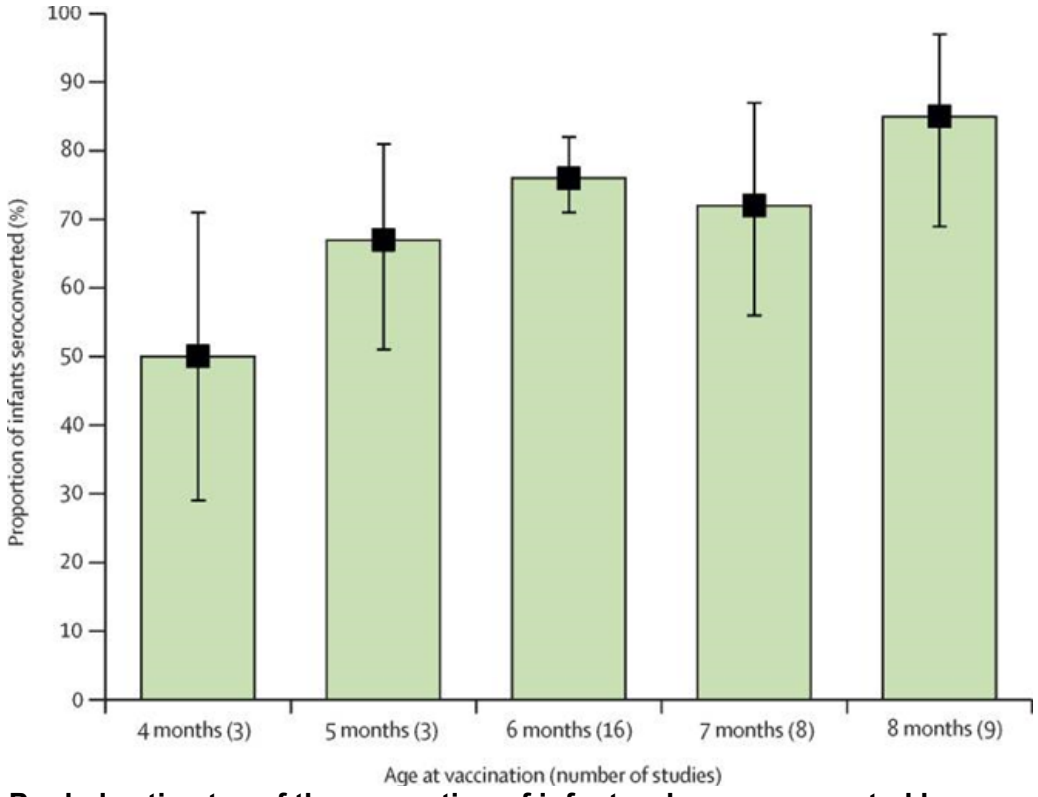


Figure 4: Pooled estimates of the proportion of infants who seroconverted by age after MCV1 vaccination.[42] Note the increasing rate of seroconversion to MCV1, from 4 to 8 months.
Image source: Nic Lochlainn et al, 2019.[42]

Ensuring the timeliness of vaccination is essential for several individual and programmatic reasons. At the individual level, early vaccination, i.e., vaccines received before the earliest or minimum valid ages, may result in suboptimal immune response due to interference with maternal antibodies.[41,42,46] For example, evidence suggests that early measles vaccination, resulted in a lack of protective antibodies levels due to neutralisation of vaccine antigen by maternal antibodies (Figure 4).[46-48] Delayed vaccination, i.e., vaccines received after the latest recommended age window, can prolong the exposure of children to potentially life-threatening VPDs such as pertussis, and measles whose peaks occur in infancy.[41,49] A previous Malawian study confirms this, showing that measles outbreaks occurred despite achieving high vaccination coverage rates, suggesting a link between the accumulation of susceptible persons and delayed vaccination.[50] Furthermore, delayed vaccination can have a domino effect, leading to further delays and non-completion of subsequent doses.[51] As a result, clusters of children with delayed or incomplete vaccinations accumulate within communities. This can ultimately lead to outbreaks of VPDs if there are enough susceptible individuals due to delayed vaccination, lack of vaccination, or suboptimal immune response to vaccination.[52-54] A marginal reduction in herd immunity can leave populations vulnerable, especially for highly infectious diseases such as measles.[52,55]

At the programmatic level, vaccinations given too early, before their earliest valid dates, or delayed, outside the recommended windows are important indicators of the quality of an

immunisation programme.[24] Early or delayed vaccination might be the only warning sign that could alert immunisation programme managers to potential problems with the delivery and uptake of certain vaccines. Monitoring the timeliness of vaccination in the population is crucial for establishing VPD risk, especially for diseases where age is linked to higher complication rates or severity. This has programmatic significance to understand the vaccination needs of specific subpopulations, target the necessary interventions, and prevent outbreaks. Timeliness also has implications for the introduction of new vaccines. For example, the WHO initially recommended an age restriction on the administration of the rotavirus vaccine, stating it should not be initiated in infants aged 12 weeks or older to minimize the potential risk of a rare but severe form of bowel obstruction called intussusception.[56] This policy recommendation restricted the introduction of rotavirus vaccine in many LMICs where untimely (i.e., early or delayed) vaccination was a major concern. However, the recommendation was subsequently reversed. Taken together, the timeliness of vaccination is a key measure of the quality of immunisation programmes. It better reflects the effective or valid coverage needed to achieve herd immunity and ensure optimal protection for individuals and communities.

1.4 The Gambia immunisation programme

The Gambia, situated in West Africa, has a population of 2.7 million people and a birth cohort of about 90,000 children who are added to the routine childhood immunisation programme yearly.[57] In 2022, the country had an under-5 mortality rate of 47.9 deaths per 1,000 births, compared to 166.5 and 113.7 deaths per 1,000 births in 1990 and 2000 respectively.[58] In May 1967, The Gambia achieved the distinction of being the first country in the world to interrupt the transmission of measles virus successfully.[59] After a yellow fever outbreak in 1978, The Gambia launched its national EPI in May 1979.[60] The programme initially offered six vaccines that targeted tuberculosis (BCG vaccine), diphtheria, pertussis, tetanus (combined DTP vaccine), measles, polio, and yellow fever. Over the past forty years, numerous additional vaccines have been introduced in The Gambia.[60] For example, the Hepatitis B vaccine (HBV) was introduced in 1986, followed by the Haemophilus influenza type B (HiB) vaccine in 1997, pneumococcal conjugate vaccine (PCV) in 2009, and inactivated polio vaccine (IPV) in 2015. More recently, in 2019, The Gambia added meningitis A (MenA) and human papillomavirus vaccine (HPV) to its routine vaccination programme. In early 2017, the country switched from a measles-only vaccine to a combined measles/rubella vaccine due to epidemiological evidence indicating the prevalence of rubella in the population. The immunisation schedule showing the recommended childhood vaccines in The Gambia is shown in **Table 1**.

Table 1: **The routine childhood immunisation schedule in The Gambia as of June 2024.**

Vaccine	Vaccination window (Timely or age-appropriate vaccination)	Early vaccination	Delayed vaccination
Hepatitis B vaccine birth dose (HepB0)	Birth	NA	> 24 hours of life[61]
Bacilli Calmette Guerin (BCG)		NA	> 7 days[60]
Oral Polio Vaccine (OPV0)			
Oral Polio Vaccine (OPV1)	2 Months (61 – 90 days)	<61 days	>90 days
Pentavalent vaccine (PENTA1)*			
Pneumococcal vaccine (PCV1)			
Rotavirus vaccine (Rota1)			
Oral Polio Vaccine (OPV2)	3 Months (91 – 120 days)	<91 days	>120 days
Pentavalent vaccine (PENTA2)*			
Pneumococcal vaccine (PCV2)			
Rotavirus vaccine (Rota2)			
Oral Polio Vaccine (OPV3)	4 Months (121 – 150 days)	<121 days	>150 days
Pentavalent vaccine (PENTA3)*			
Pneumococcal vaccine (PCV3)			
Inactivated Polio Vaccine (IPV)			
Measles and Rubella vaccine (MCV1)	9 Months (271 – 300 days)	<271 days	>300 days
Oral Polio Vaccine (OPV4)			
Yellow Fever vaccine			
Meningitis A vaccine	12 months	NA**	NA**
Measles and Rubella vaccine (MCV2)	18 months	NA**	NA**
Interval between multi-series vaccine: e.g., OPV1 – OPV2; OPV2 – OPV3; PENTA1 – PENTA2; PENTA2 – PENTA3	4 – 8 weeks (28 – 56 days)	<4 weeks or 28 days**	>8 weeks or 56 days**

Note: *****Pentavalent vaccine protects against Diphtheria, Tetanus, Pertussis, Hepatitis B, and Haemophilus influenza type B (DPT-HepB-HiB). **There is no strict window around the vaccines given in the second year of life (i.e., 12 months and above) in The Gambia. OPV booster is also given at 18 months in The Gambia.

The Gambian EPI is primarily funded by government budgetary allocation,[60] but supplemented through additional funding and support from the WHO, UNICEF, Gavi the Vaccine Alliance and other development partners.[62] All routine childhood vaccines are provided free of charge in the country. Vaccination services are implemented through two approaches - fixed base (health facility) delivery and mobile outreach clinics that cater to children in communities without functional health facilities. Since its inception in 1979, The Gambian EPI programme has grown to be a highly successful and model immunisation programme in sub-Saharan Africa. For more than a decade, The Gambia EPI has consistently maintained vaccination coverage rates comparable to those achieved in high-income countries. The country consistently achieved coverage rates above 90% for several vaccines,[63] including DTP3 which is traditionally regarded as the measure of national immunisation programme performance (figure 5). The country achieved the GVAP vaccination coverage target a decade early,[64,65] and is on track to reach the coverage target of the WHO IA2030.[9] The success of The Gambia EPI can be attributed, in parts, to high public awareness

about the benefits of vaccines,[66] and easy access to vaccination services through fixed Reproductive and Child Health and outreach clinics for remote rural communities.[67]

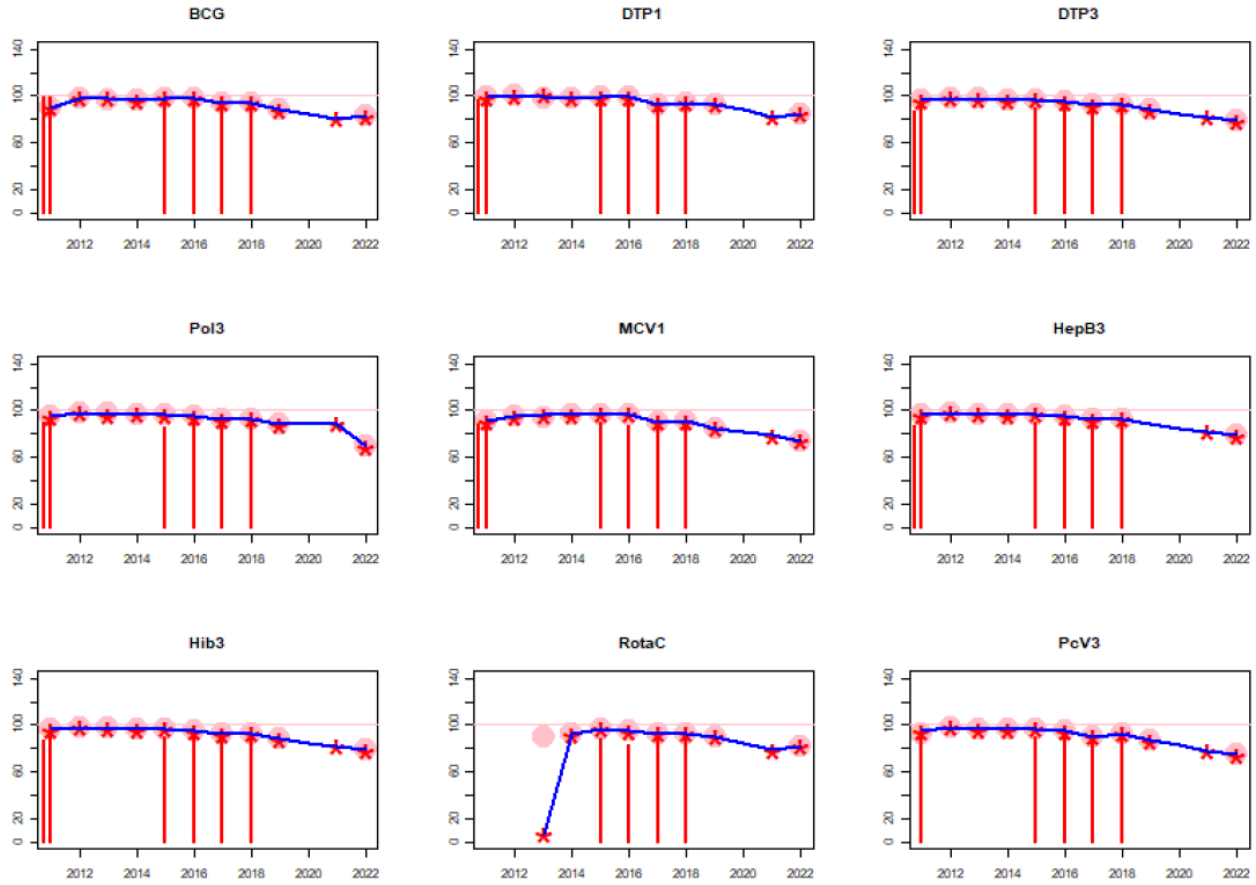


Figure 5: **WHO and UNICEF estimates of routine childhood vaccination coverage in The Gambia, 2011 – 2022**.
Image source: World Health Organization, 2023.[63]

Despite the notable successes, many poor, rural, and hard-to-reach communities continue to have low vaccination coverage rates. In fact, national immunisation coverage rates for many vaccines have remained stagnant since 2009.[68] Furthermore, the global COVID-19 pandemic, which began in The Gambia in March 2020, may have further contributed to a decline in routine vaccination coverage across the country (Figure 5). Even before the onset of the COVID-19 pandemic, there was evidence that a large proportion of vaccinations were delayed and not given according to recommended timeframes.[67,69,70] These issues are concerning, particularly in light of recent measles outbreaks in some parts of the country. In fact, there has been a six-fold increase in measles cases as of mid-2023 compared to 2020 figures (Figure 6), despite historically high coverage of MCV1 and the introduction of the second dose of measles-containing vaccine (MCV2) since 2012.[71,72] Measles outbreaks are often a sign of emerging immunity gaps in vaccination programmes. Several factors, including postponed measles campaigns, stagnating or declining measles vaccine coverage, and untimely (early and delayed) measles vaccination potentially explain the recent trend of increasing outbreaks. These factors can lead to the accumulation of susceptible children in spatial clusters, increasing the risk of outbreaks. Given the continued

addition of new vaccines to the immunisation schedule, The Gambia's EPI faces the challenge of delivering all recommended vaccines in a timely and age-appropriate manner.

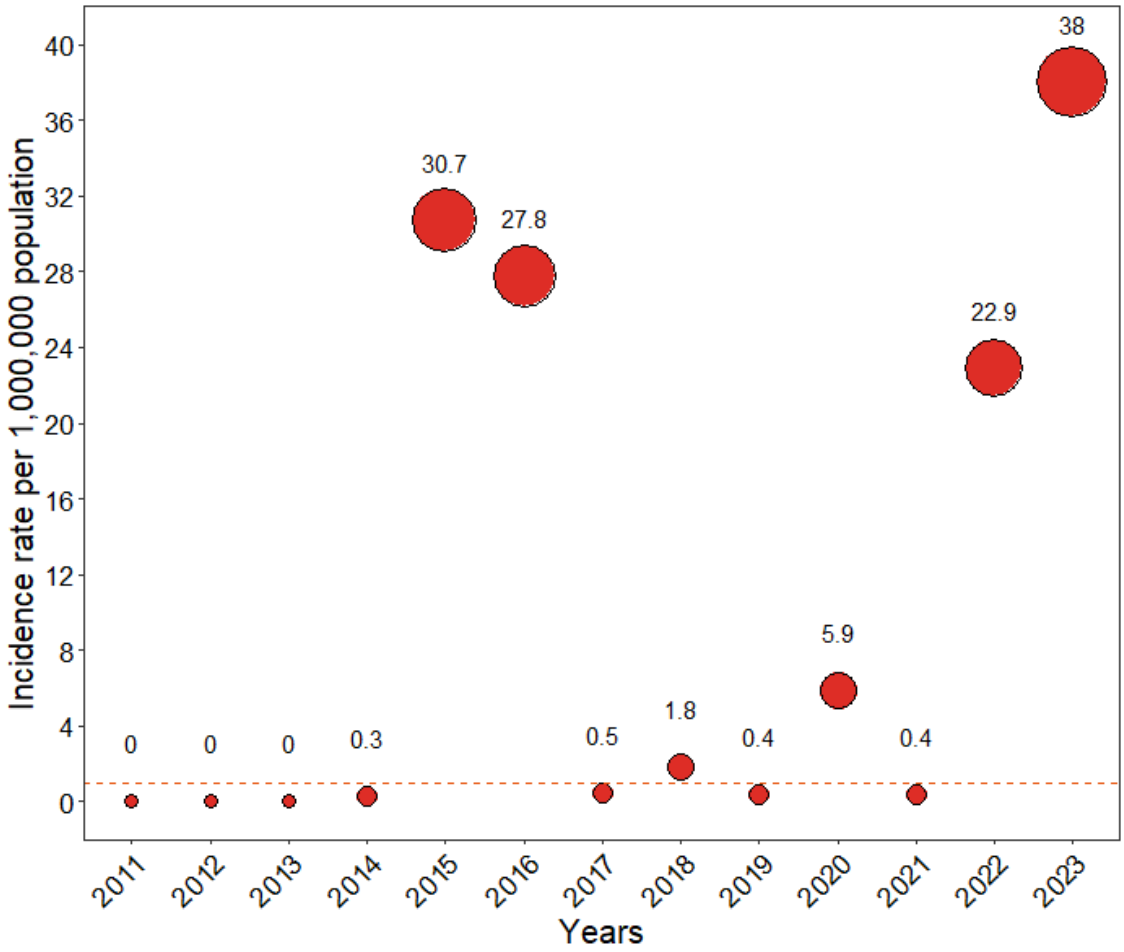


Figure 6: Annual measles incidence rate per million population in The Gambia, 2011-2023.
Note: the red horizontal dashed line is the WHO threshold for measles elimination of ≤1 case per 1,000,000 population.
Data source: World Health Organization, 2023.[71] **Image credit:** Oghenebrume Wariri.

1.5 Existing literature on the timeliness of childhood vaccinations in The Gambia

In The Gambia, three studies, published in 2014,[67] 2015,[70] and 2016[69] have so far assessed the timeliness of routine childhood vaccination. These studies revealed that although the overall vaccination coverage was high for the vaccines studied, a large proportion of children did not receive vaccinations according to the antigen-specific, nationally recommended vaccination timeframes. While these studies focused mainly on delayed vaccination, they did not adequately explore other crucial dimensions such as early vaccination and untimely intervals between subsequent doses of multi-series vaccines like pentavalent vaccines. This one-dimensional approach provides inadequate data to gain a holistic understanding of the overall pattern of vaccination timelines in The Gambia. Moreover, the previous studies used a pragmatic approach that lumped together and categorised all children vaccinated after the latest recommended vaccination timeframe as "delayed vaccination", irrespective of the numbers of days they were

delayed. This methodological approach prevents a nuanced interpretation of the outcome. Communities where children experience a longer average number of days vaccinations are delayed may face an increased risk of exposure to VPDs and potential outbreaks compared to communities where delays are shorter.

The definition of timely vaccination was not consistent across the three studies. The timeframes that were considered untimely vaccination in one study were classified as timely and age-appropriate vaccination in the other studies. This methodological approach limits the comparability of their findings. Moreover, none of the studies used a nationally representative dataset, thus, provide an incomplete picture of the true scale of vaccination timeliness in The Gambia. While these studies explored several factors that may explain the untimely receipt of childhood vaccination, they primarily focused on demand-side factors such as parental and childhood sociodemographic characteristics as determinants of timeliness. However, there is evidence from various sub-Saharan African settings that supply-side factors such as geographic accessibility to immunisation clinics determine the uptake of childhood vaccination.[73,74] Factors such as how far a family lives from a vaccination clinic, how long they had to travel for an appointment, and the presence (or lack thereof) of accessible roads can all impact the uptake of health services, including vaccination. The absence of comprehensive evidence regarding the broader determinants hinders an understanding of the complex interplay between different demand and supply-side factors and their potential influence on timely vaccination.

Finally, it is worth noting that the previous studies on vaccination timeliness in The Gambia did not generate spatially disaggregated estimates; rather, they produced overall estimates. This omission meant that the studies missed the opportunity to identify specific areas or “hotspots” of too early or delayed vaccinations. While the estimates from these studies are a crucial initial step in exploring vaccination timeliness, they are insufficient for targeted programmatic interventions because they did not identify pockets of vulnerabilities that could benefit from targeted interventions. Taken together, the identified gaps in the existing studies on vaccination timeliness in The Gambia limit the comparability, programmatic relevance, and the extent to which inference can be drawn from their findings.

1.6 Rational for the PhD studies

Routine childhood vaccination programmes are fundamental to public health, especially in LMICs, where preventable diseases still pose significant threats to children’s well-being. While vaccination coverage rate have traditionally been used to measure immunisation programme performance, recent studies have recognised the limitations of relying solely on this metric. For instance, a recent Global Burden of Disease Study suggested that vaccination timeliness should be taken into account when evaluating coverage trends.[75] The authors recommended that future research

should develop methods to estimate age-specific vaccination coverage where data permit. They argue that such estimates could provide a better reflection of schedule adherence and identify when delays in vaccination are occurring.[75] In addition, a 2019 WHO white paper on harmonising vaccination coverage measures also recognised that vaccination timeliness is a better indicator of effective or valid coverage.[26] The white paper emphasised that valid or timely coverage reflects vaccine doses that are most likely to be immunogenic. This is based on respecting the timing in the national schedule, including the child's age and the minimal interval between doses.[26]

The Gambian routine childhood immunisation programme can be considered 'maturing.' In contrast to many sub-Saharan African countries, it has consistently achieved relatively high vaccination coverage rates over the past decade, comparable to those of many high-income countries. Despite being regarded as a model for other LMICs,[64,65] documented evidence shows that the country still faces significant challenges in delivering vaccines within the recommended timeframes.[67,69,70] Additionally, there has been an increasing trend of VPDs outbreaks, particularly measles.[71,72] In 2022 and 2023, the measles incidence rates were 22.9 and 38 cases per million population (Figure 6), respectively, compared to the WHO elimination benchmark of <1 case per million.[76] For more than a decade before the COVID-19 pandemic, vaccination coverage plateaued, and over the past three years, there has been a decline in coverage for many routine vaccines.

The emerging weaknesses in ensuring timely coverage, repeated measles outbreaks, and declining coverage might have been detected earlier if indicators of effective or timely coverage were also prioritised alongside overall coverage measures. Neglecting to measure quality indicators such as timeliness can obscure the onset of programme weaknesses. The underlying maturity of the immunisation programme, along with its emerging weaknesses and the unique characteristics of The Gambia, such as its relatively small population and geography, make it a suitable study site for this PhD. When successfully implemented, the findings and methodologies developed during this PhD can be adapted to other countries with 'maturing' immunisation systems, enabling early detection of programme weaknesses.

In the last decade, there has been a notable increase in studies exploring the timeliness of childhood vaccination in LMICs.[77] However, a review of the existing studies from The Gambia shows that there are important methodological and measurement gaps that limit their programmatic relevance. This PhD research will address these gaps by comprehensively examining the burden, spatial patterns, and gain a better understanding of the broader factors influencing vaccination timeliness in The Gambia. By examining the various dimensions of timeliness, and addressing other identified gaps, this research seeks to fill a crucial void in the existing literature and inform targeted interventions to enhance the effectiveness of immunisation programmes in The Gambia and similar LMIC settings. The PhD research will potentially lay the

groundwork for evidence-based interventions to address untimely childhood vaccination in The Gambia.

Moreover, the COVID-19 pandemic has introduced unprecedented disruptions to healthcare systems worldwide, potentially exacerbating existing challenges in timely vaccine delivery and uptake. Understanding the pandemic's impact on vaccination timeliness is paramount for mitigating its adverse effects and ensuring the resilience of The Gambia immunisation programme in the face of future public health emergencies. This PhD plans to examine the impact of the COVID-19 pandemic on the timeliness of childhood vaccination in The Gambia through a detailed analysis of longitudinal data spanning pre-pandemic and pandemic periods. By shedding light on the potential vulnerabilities exposed by the pandemic, this PhD research holds profound implications for strengthening health systems' capacity to respond to emergent threats and safeguarding the health of vulnerable populations.

Chapter 2: The PhD Aim, Hypothesis, Objectives and Methodology

2.1 Aim

The overarching aim of this study was to investigate the burden and spatial pattern of the various dimensions of the timeliness of childhood vaccination in The Gambia and examine the influence of both demand-side and supply-side factors and the COVID-19 pandemic.

2.2 Hypotheses

1. Despite an expected high overall vaccination coverage rate, various dimensions of untimely childhood vaccination, including early, delayed, and untimely intervals between doses, are likely to be prevalent in The Gambia.
2. The prevalence of untimely vaccinations in The Gambia will demonstrate obvious subnational inequalities, with districts in the more rural regions of the country being more likely to experience higher *'un-timeliness'* for all vaccines scheduled for the first year of life.
3. The COVID-19 pandemic will result in a significant increase in the proportion of untimely childhood vaccinations, as well as a decrease in routine childhood vaccination coverage in The Gambia, particularly during the peaks of epidemiological waves.
4. The most common factors influencing the timeliness of childhood vaccination in The Gambia will be household factors such as socioeconomic and demographic characteristics, which determine the household's intention or recognition of the need for vaccination.
5. Factors impacting a household's ability to reach immunisation facilities, such as geographic accessibility or travel time, will have an impact on the timeliness of receiving childhood vaccinations in The Gambia.
6. Factors determining the readiness of immunisation facilities to deliver appropriate services such as ownership of functional cold storage facility or staffing numbers, will have an impact on the timeliness of receiving childhood vaccinations in The Gambia.

2.3 Specific Objectives

The four specific objectives of the PhD research are:

1. To systematically review the existing empirical literature on the timeliness of routine childhood vaccination in low-and middle-income countries, with the aim of identifying the measurement and methodological gaps to inform the design of the PhD research.
2. To describe the burden and the spatial pattern of the various dimensions of the timeliness of childhood vaccination in The Gambia.

3. To determine the impact of the COVID-19 pandemic on the timeliness and coverage of routine childhood vaccination in the Gambia.
4. To examine the influence of demand-side factors such as individual and family sociodemographic characteristics, as well as supply-side factors such as geographic accessibility to immunisation clinics and the readiness of these clinics to deliver services on the timeliness of receiving routine childhood vaccination in The Gambia.

2.4 Methodology

During my PhD, I employed a broad range of established methodologies, including various datasets, analytic and statistical approaches, to appropriately address the four objectives described above. The datasets used, the analytical and statistical techniques employed are described in detail in the respective research papers and accompanying supplementary appendices. Broadly, these research methodologies can be broken down into five components, as shown in the overview below. **Table 1** maps the datasets, analytical and statistical approaches adopted to each of the PhD objective.

2.4.1 Scoping Review of the empirical literature of vaccination timeliness

To identify measurement and methodological gaps in the existing research on the timeliness of vaccination and inform the design of my PhD research, I conducted a scoping review, following the guidance framework described by the *Joanna Briggs Institute*. I searched five electronic databases for peer-reviewed articles in English and French that examined vaccination timeliness in LMICs, and were published from database inception until 01 July 2021. Paper 1 (included as appendix), is the review protocol and provides the detailed methodology, including the search strategy, data extraction approach, and analytic approach. Paper 2 outlines the results of the methodological and measurement gaps synthesised from the empirical literature on vaccination timeliness. Paper 2 addresses Objective 1 and is presented in Chapter 3.

2.4.2 Geospatial Modelling

To address Objective 2 of my PhD research, which involved describing the burden and spatial pattern of the various dimensions of the timeliness of childhood vaccination in The Gambia, I utilised a fully Bayesian geostatistical modelling approach. In this well-established geospatial modelling approach, I incorporated publicly available spatial covariates to increase predictive accuracy. By using this approach, I mapped the various dimensions of vaccination timeliness across The Gambia at a resolution of 1 × 1-km2 pixel. To do this, I utilised cluster-level childhood vaccination data from The Gambia 2019–20 DHS. In Paper 4 and the accompanying supplementary appendix, I provide a detailed description of this methodology and my findings. This paper is included along with Paper 3 in Chapter 4 of my thesis. Paper 3 presents a descriptive

analysis of the burden of the different dimensions of the timeliness of vaccination in The Gambia. Together, these papers address Objective 2 of my PhD research.

2.4.3 Interrupted time-series analysis

To address objective 3 of my PhD, which involved determining the impact of the COVID-19 pandemic on the timeliness and coverage of routine childhood vaccination in the Gambia, I implemented a binomial interrupted time-series regression modelling approach. To achieve this, I obtained prospective monthly birth cohort data of about 60,000 children in over 300 communities in two large Health and Demographic Surveillance System in The Gambia, including data from the pre-pandemic period (January 2015–February 2020) and the three waves of the pandemic period (March 2020–December 2021). In Paper 5, which is presented in chapter 5, I provided a detailed description of the binomial interrupted time-series regression modelling approach used to analyse the data and presents the findings from this analysis.

2.4.4 Travel time modelling (i.e., geographic accessibility to clinics)

To examine the influence of supply-side factors on the timeliness of receiving routine childhood vaccination in The Gambia, I estimated travel time to the nearest immunisation clinic, using *AccessMod*, a WHO tool to model physical accessibility. Travel times were modelled as the least cost path over an impedance surface. I incorporated various spatial covariates, road network data and cluster geolocation (i.e., longitude and latitude) from The Gambia 2019–20 DHS for this modelling process. The nearest clinic was determined using data from the national immunisation facility mapping and census conducted by The Gambia EPI. The travel time outputs (i.e., intermediate outputs) were incorporated with other supply-side factors to address objective 4 of my PhD. Chapter 6 of my thesis (or Paper 6) presents a detailed description of this methodology and the multi-level modelling approach used to achieve objective 4.

2.4.5 Multi-level regression modelling

Investigating the influence of demand- and supply-side factors on timely childhood vaccination in The Gambia (Objective 4) required a robust analytical approach. I employed a Bayesian multi-level binary logistic regression model, leveraging two nationally representative datasets: the 2019-20 The Gambia DHS and the national immunisation facility mapping and census. To capture additional crucial supply-side factors, I collaborated with The Gambia EPI to update the national immunisation facility mapping and census dataset with additional information on the number of times each facility is open per month, staffing levels, and other relevant variables. A detailed description of the Bayesian multi-level binary logistic regression modelling approach adopted to achieve objective 4, and the accompanying findings can be found in Paper 6, as presented in Chapter 6 of this thesis.

Table 1: Mapping the datasets, analytical and statistical approach utilised to achieve each PhD objective.

		Datasets					Analytical and statistical approach					
	PhD objective	**Empirical literature (1970 - 2021)**	**Longitudinal cohort HDSS data (2015 - 2021)**	**Cross-sectional The Gambia DHS & spatial location data (2019/2020)**	**National immunisation facility census and spatial location data (2019)**	**Spatial covariates**	**Scoping review**	**DHS direct survey method**	**Spatial modelling**	**Time-series analysis**	**Travel time modelling**	**Multi-level regression**
OBJ 1.	To systematically review the available empirical literature on the timeliness of routine childhood vaccination in low-and middle-income countries, with the aim of identifying the measurement and methodological gaps to inform the design of the PhD research	✓					✓					
OBJ 2.	To describe the burden and the spatial pattern of the various dimensions of the timeliness of childhood vaccination in The Gambia.			✓		✓		✓	✓			
OBJ 3.	To determine the impact of the COVID-19 pandemic on the timeliness and coverage of routine childhood vaccination in the Gambia.		✓							✓		
OBJ 4.	To examine the influence of demand-side factors such as individual and family sociodemographic characteristics, as well as supply-side factors such as geographic accessibility to immunization clinics and the readiness of these clinics to deliver services on the timeliness of receiving routine childhood vaccination in The Gambia.			✓	✓	✓					✓	✓

Note: HDSS = Health and Demographic Surveillance System; **DHS** = Demographic and Health Survey. **Descriptive analysis** refers to the DHS Direct Survey Methodology applied to generate vaccination coverage estimates that are aligned to those published by the DHS. The same methodology was used to generate the prevalence of the various dimensions of vaccination timeliness.

2.5 Ethics

This research received ethical approval from both the Research Ethics Committee of the London School of Hygiene and Tropical Medicine (LSHTM) (Ethics Ref: 22786; Date: January 20, 2021) and The Gambia Government and MRC Unit The Gambia at LSHTM Joint Ethics Committee (Project ID/Ethics ref: 22786; Date: January 16, 2021). All participants of the studies provided informed consent to participate, and all personal identifiers were removed from the datasets which were analysed. Copies of the ethical approval certificates are available as Appendix 11 and Appendix 12.

2.6 Funding

This thesis is a product of research funded by the EDCTP2 Programme, supported by the European and Developing Countries Clinical Trials Partnership (EDCTP). The project was made possible through a 33-month Career Development Fellowship (grant number: TMA2019CDF-2734 – TIMELY) awarded to me, Oghenebrume Wariri, which spanned from 1st November 2020 to 31st July 2023. This fellowship aims to empower early- to mid-career researchers by providing opportunities to build research expertise and skills. Additionally, I received further funding from a 15-month Wellcome Trust Institutional Strategic Support Fund (ISSF) grant (RSRO_P67869) administered through Imperial College London from 01 November 2020 to 28 February 2022.

2.7 Dissemination

Between 2021-2024, I have made various efforts to disseminate and present the research findings from this PhD. **Table 2** describes the activities undertaken.

2.8 Availability of Codes

To ensure transparency and reproducibility, the R codes which I wrote and used for data cleaning, wrangling, and analysis to achieve all the PhD objectives has been deposited in a publicly accessible open repository. Links to the specific GitHub repositories containing these R scripts are provided in Appendix 13.

Table 2: Dissemination activities undertaken during the PhD Programme to share research findings

S/no.	Title of talk and format	Organisation / Event	Audience
1	Timeliness Matters: examining the burden and the spatial pattern of untimely childhood vaccinations in The Gambia. (**Oral presentation**)	MRC Unit The Gambia at LSHTM Academic Seminar Series. **The Gambia**. June 2023	Academic audience
2	Timeliness Matters: examining the burden and the spatial pattern of untimely childhood vaccinations in The Gambia (**Oral presentation and panel discussion sessions**)	Dissemination workshop for the TIMELY Project to Immunisation Stakeholders in **The Gambia**. July 2023	WHO, UNICEF, National and Regional programme managers of the Expanded Programme on Immunisation in The Gambia
3	Leveraging multiple sources of data to characterise vaccination programme weakness. (**Oral presentation and panel discussion**)	Princeton University, Office of Population Research (OPR), Vaccination Meeting, **Princeton, USA**. October 2023	Academic, UNICEF, and Equity Reference Group for Immunisation
4	Mapping the timeliness of routine vaccination among 12-35 months old children in The Gambia: a spatial modelling study (**Poster presentation**)	11th European and Developing Countries Clinical Trials Partnerships (EDCTP) Conference, **Paris, France**. November 2023	Academic, Non-governmental organisations (NGOs), and donor agencies
5	Timeliness of routine childhood vaccination among 12-35 months old children in The Gambia: analysis of national immunisation survey data, 2019-2020. (**Oral presentation**)	European Congress of Tropical Medicine and Hygiene (ECTMIH2023), **Utrecht, Netherlands**. November 2023	Academic, NGOs, and donor agencies
6	The timeliness of routine childhood vaccination in The Gambia: mapping the spatial pattern (**Research Masterclass oral presentation**)	42nd Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID2024), **Copenhagen, Denmark**. May 2024	Academic audience

PART 2: ANALYTICAL CHAPTERS

Immunisation facilities in The Gambia
Image source: Photographs taken by Oghenebrume Wariri during facility mapping

Chapter 3: Identifying the measurement and methodological gaps in the empirical literature on the timeliness of routine childhood vaccination in low-and middle-income countries (Research Paper)

3.1 Overview of Chapter

This chapter addresses the first objective of my PhD which was; "*To systematically review the available empirical literature on the timeliness of routine childhood vaccination in low-and middle-income countries, with the aim of identifying the measurement and methodological gaps to inform the design of the PhD research*".

As highlighted in the introduction, three empirical studies so far have investigated the timeliness of routine childhood vaccination in The Gambia. However, these studies are limited by key measurement and methodological gaps that hinder their comparability and utility. In this chapter, I utilised a scoping review approach, a well-established research methodology, ideal for mapping the extent , range, nature and identifying gaps in the literature on a specific topic. This approach allowed me to systematically examine existing studies on the timeliness of routine childhood vaccination in LMICs, specifically focusing on identifying their measurement and methodological gaps. The insights gained from this scoping review played a crucial role in shaping the design of my subsequent PhD studies.

This scoping review was published in PLoS Global Public Health, with the following full bibliographic information:

Wariri O, Okomo U, Kwarshak YK, Utazi CE, Murray K, Grundy C, Kampmann B. (2022) Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps. PLOS Glob Public Health.

This chapter is supplemented by the full scoping review **protocol paper**, which was published in PLoS ONE and is included as **Appendix 1**. The search strategy, summary characteristics of included studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist accompanying this scoping review paper are also included as **Appendix 2**, **Appendix 3** and **Appendix 4**.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1509291	**Title**	DR
First Name(s)	Oghenebrume		
Surname/Family Name	Wariri		
Thesis Title	Timeliness of routine childhood vaccination in The Gambia: examining the burden, spatial pattern, determinants and the impact of COVID-19 pandemic		
Primary Supervisor	Chris Grundy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS Global Public Health		
When was the work published?	July 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?
Please list the paper's authors in the intended authorship order:

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised this study and led it's execution. I conducted the comprehensive systematic literature review across five electronic databases, screened titles, abstracts, and full texts. I extracted relevant data, performed the data analysis, and interpreted the results. I wrote the initial manuscript draft and handled all referencing. I handled the submission, the reviewer responses, and the re-submisison process.

SECTION E

Student Signature	[redacted]
Date	20th February 2024

Supervisor Signature	Chris Grundy
Date	21 Feb 2024

PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps

Oghenebrume Wariri[1,2,3]*, **Uduak Okomo**[1], **Yakubu Kevin Kwarshak**[4], **Chigozie Edson Utazi**[5,6], **Kris Murray**[7,8], **Chris Grundy**[2‡], **Beate Kampmann**[1,3‡]

1 Vaccines and Immunity Theme, MRC Unit The Gambia at London School of Hygiene and Tropical Medicine, Fajara, The Gambia, **2** Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom, **3** Vaccine Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom, **4** Department of Surgery, Jos University Teaching Hospital, Plateau State, Nigeria, **5** WorldPop, School of geography and Environmental Science, University of Southampton, Southampton, United Kingdom, **6** Southampton Statistical Sciences Research Institute, University of Southampton, Southampton, United Kingdom, **7** MRC Unit The Gambia at The London School of Hygiene and Tropical Medicine, Fajara, The Gambia, **8** MRC Centre for Global Infectious Disease Analysis, Imperial College School of Public Health, Imperial College London, London, United Kingdom

‡ CG and BK are joint senior authors on this work.
* Oghenebrume.Wariri@lshtm.ac.uk

OPEN ACCESS

Citation: Wariri O, Okomo U, Kwarshak YK, Utazi CE, Murray K, Grundy C, et al. (2022) Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps. PLOS Glob Public Health 2(7): e0000325. https://doi.org/10.1371/journal.pgph.0000325

Editor: Karen D. Cowgill, University of Washington, UNITED STATES

Received: December 16, 2021

Accepted: June 14, 2022

Published: July 14, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pgph.0000325

Data Availability Statement: All related data are included in the mansucript or in the supplementary file.

Abstract

Empiric studies exploring the timeliness of routine vaccination in low-and middle-income countries (LMICs) have gained momentum in the last decade. Nevertheless, there is emerging evidence suggesting that these studies have key measurement and methodological gaps that limit their comparability and utility. Hence, there is a need to identify, and document these gaps which could inform the design, conduct, and reporting of future research on the timeliness of vaccination. We synthesised the literature to determine the methodological and measurement gaps in the assessment of vaccination timeliness in LMICs. We searched five electronic databases for peer-reviewed articles in English and French that evaluated vaccination timeliness in LMICs, and were published between 01 January 1978, and 01 July 2021. Two reviewers independently screened titles and abstracts and reviewed full texts of relevant articles, following the guidance framework for scoping reviews by the Joanna Briggs Institute. From the 4263 titles identified, we included 224 articles from 103 countries. China (40), India (27), and Kenya (23) had the highest number of publications respectively. Of the three domains of timeliness, the most studied domain was 'delayed vaccination' [99.5% (223/224)], followed by 'early vaccination' [21.9% (49/224)], and 'untimely interval vaccination' [9% (20/224)]. Definitions for early (seven different definitions), untimely interval (four different definitions), and delayed vaccination (19 different definitions) varied across the studies. Most studies [72.3% (166/224)] operationalised vaccination timeliness as a categorical variable, compared to only 9.8% (22/224) of studies that operationalised timeliness as continuous variables. A large proportion of studies [47.8% (107/224)] excluded the data of children with no written vaccination records irrespective of caregivers' recall of

Funding: This project is part of the EDCTP2 Programme supported by the European and Developing Countries Clinical Trials Partnership (grant number TMA2019CDF-2734 - TIMELY). OW is also supported by an Imperial College London Wellcome Trust Institutional Strategic Support Fund (ISSF) (grant no RSRO_P67869). KM is supported by joint Centre funding from the UK Medical Research Council and Department for International Development [MR/R0156600/1]. CEU is supported by funding from the Bill & Melinda Gates Foundation (Investment ID INV-003287). The Vaccines and Immunity Theme (OW, UO, and BK) is jointly funded by the UK MRC and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 Programme supported by the EU (MC UP_A900/1122, MC UP A900/115). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist

their vaccination status. Our findings show that studies on vaccination timeliness in LMICs has measurement and methodological gaps. We recommend the development and implement of guidelines for measuring and reporting vaccination timeliness to bridge these gaps.

Introduction

Since its inception in 1974, the expanded programme on immunisation (EPI) has successfully decreased the incidence of, and mortality from childhood vaccine preventable diseases (VPDs), nevertheless, progress has plateaued, or regressed in many countries [1]. Vaccination coverage dropped globally by about 3% between 2019–2020, with an estimated 23 million children under the age of one year not receiving their basic vaccines in 2020 –the highest number since 2009 [2]. In addition, 8·9 million children were not routinely vaccinated with the first-dose measles-containing vaccine (MCV1) which prevent measles, a highly contagious infectious disease [3]. Disruptions to routine childhood vaccination due to the ongoing pandemic are likely to amplify the already existing gaps which prevented countries from reaching global immunisation targets [4].

The traditional metric used for evaluating the success of immunisation programs is vaccine-specific crude vaccination coverage [5]. Crude vaccination coverage conceptually assumes uptake of vaccines without considering timely delivery, i.e., whether doses are received within the recommended window, are too early, delayed, or whether the intervals between doses are inappropriate [6]. To achieve the full benefit of vaccines, however, both high coverage and timely delivery are required. Timeliness of vaccination–i.e., vaccination received within the recommended window, in an age-appropriate manner explores the quality dimension of immunisation programs and is important for several reasons. Untimely vaccination might be the only early warning sign that could alert EPI programme managers to potential problems with the delivery of certain vaccines, and help put in place mitigating strategies. Vaccines received too early, or before the earliest valid ages may result in suboptimal immunity due to interference with maternal antibodies [7]. Delayed vaccination, on the other hand, prolongs the exposure of children to debilitating VPDs such as *Haemophilus influenzae* type b, pertussis, and measles whose peaks occur in infancy [7, 8]. Delayed vaccination also increases a child's risk of not completing their schedule, and ultimately leads to suboptimal levels of herd immunity needed to prevent the outbreak of VPDs. There is evidence suggesting that measles outbreaks have occurred in the past due to delayed vaccination despite high overall crude vaccination coverage [9].

Over the last decade, studies exploring vaccination timeliness have gained some traction [10]. A recent Global Burden of Disease Study published in *The Lancet* argued that vaccination timeliness better reflects coverage trend, thus, recommended that future research should estimate age-specific vaccination coverage rather than crude coverage alone [11]. Most vaccination timeliness studies have been conducted in high-income countries (HICs) with much fewer reports from low-and middle-income countries (LMICs) where vaccination coverage is variable but comparatively lower, and VPD burden is high [10]. There is emerging evidence suggesting that the published studies on the timeliness of routine vaccination in LMICs has key methodological and measurement issues that limit their comparability, utility, and the extent to which inference can be drawn from their findings [10]. Hence, there is an urgent need to identify, and document these measurement and methodological gaps which could

inform the design, conduct, and reporting of future research on the timeliness of routine childhood vaccination in LMICs.

This scoping review, therefore, aimed to identify and synthesise published literature on the timeliness of routine childhood vaccination in LMIC and answer the following questions: (a) how has the literature on vaccination timeliness evolved?; (b) how has vaccination timeliness been defined or operationalisation?; (c) what domains of vaccination timeliness have been studied; (d) what methodological or statistical approaches have previous studies deployed to ensure robustness of results and; (e) what determinants of untimely vaccination have been explored.

Materials and methods

Scoping reviews are an emerging approach for evidence synthesis. Unlike systematic reviews that traditionally answer precise questions related to the effectiveness of a specific intervention, scoping reviews are exploratory in nature [12]. Scoping reviews typically address a broad question such as what kind of evidence exists on a topic, and how research on that topic has been designed or conducted [13]. They are useful in mapping the key concepts underpinning a research area as well as to clarify working definitions or concepts, and identify knowledge gaps [12]. These characteristics make the scoping review approach well suited to answer our research questions aimed at identifying methodological and measurement gaps in vaccination timeliness studies (Box 1). Although conducted for different purposes compared to systematic reviews, scoping reviews still require rigorous and transparent methodologies to ensure that their results are trustworthy [13].

Box 1. Potential measurement and methodological gaps in vaccination timeliness studies

There are important issues that must be considered during data collection, analysis, and presentation of results in vaccination timeliness studies to ensure robustness and comparability of results. We refer to the key issues related to the collection of data and analysis as 'methodological gaps', while those related to how results are presented as 'measurement gaps'.

Methodological gaps

1. How missing vaccination dates are handled: to effectively generate robust estimates for vaccination timeliness, precise vaccination dates are required. Inadequately handling missing dates is a potential gap
2. Definition of vaccination timeliness: to be able to compare results or generate point estimates from multiple studies, uniformity in defining vaccination timeliness is desirable.

Measurement gaps

1. Operationalisation of vaccination timeliness: how timeliness is reported or operationalized (continuous vs categorical) determines the usefulness of the estimates produced.

2. Domains of vaccination timeliness studied: domains of timeliness includes; 'early', 'untimely interval', or 'delayed' vaccination. focusing on one domain without the other is a potential measurement gap.
3. Determinants of vaccination timeliness: several factors act as barriers to receiving vaccines in a timely age-appropriate manner. Narrowly focusing on a few determinants could be considered a measurement gap.

This scoping review was based on the guidance framework of the Joanna Briggs Institute (JBI) [14]. The review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (S1 Checklist) [15]. Since registration of scoping reviews are currently not accepted in PROSPERO, we published the review protocol *a priori* in a peer-review journal [16]. The review process did not deviate from the previously published protocol.

Search strategy

The literature search was performed across the databases: MEDLINE, EMBASE, Global Health, CINAHL and Web of Science. Following the recommendation of the JBI, we followed a three-step search strategy to ensure a comprehensive search [17]. First, a preliminary search of MEDLINE and Web of Science was conducted on March 27, 2021 using the key search concepts: *Childhood vaccination*; *Timeliness*; and *LMICs*. We refined the initial search strategy by including additional key concepts after analysing the text words in the title and abstract of the retrieved papers, and the indexing terms. The search strategy was developed in consultation with a Librarian and was refined based on their input. The full search strategy and search terms used in MEDLINE is included as S1 Table. In the second step, we conducted a full search on July 01, 2021, across all five included databases using the refined search strategy from the first step. The search strategy was adapted to fit the search terminologies for each database. In the third step, we searched the reference list of the included papers (from the database search) for additional sources not previously retrieved.

Inclusion criteria

Studies were included if they reported childhood vaccinations that are part of the routine national EPI schedules; calculated any measure of timeliness related to vaccine coverage; are based on data from countries categorised as LMICs (low-income, lower middle-income, and upper-middle income economies) according to 2020 World Bank classification; [18] were published in English or French languages from 01 January 1978 through to July 01,2021. We restricted the review to studies conducted in LMICs because these countries account for a higher proportion of the global burden of VPDs, and the national EPI schedule in these countries generally adopts the WHO-recommended childhood immunization schedule. We did not include grey literature because it was unmanageable to manually search for additional official reports on vaccination timeliness from the EPI website of the more than 120 listed LMICs. We included studies published from 01 January 1978 because routine childhood immunization against diphtheria, pertussis, tetanus, poliomyelitis, measles, and tuberculosis commenced in LMICs in 1977 [1]. The search was extended to July 01,2021 to capture up-to-date evidence

on timeliness of routine childhood vaccination. We excluded systematic reviews, study protocols, journal commentaries, and conference papers.

Study selection

Retrieved titles were imported into Endnote X9.3.3 (Clarivate Analytics) for de-duplication of records. Subsequently, the records were exported to Rayyan–a novel web based application for screening articles for reviews [19]. Two reviewers (OW and YKK) independently screened the titles and abstracts for relevance using the pre-set eligibility criteria. Records that met the eligibility criteria were exported back to Endnote for full-text retrieval, screening, and extraction. One reviewer (OW) screened the full text of records to ensure they were appropriate for full data extraction while another reviewer (YKK) verified all decisions. Final decisions regarding the eligibility of articles were made through consensus. A third member of the review team (UO) was consulted to resolve disagreements when the two initial reviewers fail to reach a consensus. All decisions were based on consensus.

Data extraction. We used a data extraction template to extract the information of interest from the included articles. We adapted the template from the JBI data extraction tool for scoping reviews [20]. Before the commencement of data extraction, two members of the review team piloted the extraction template on 20 randomly selected articles and was subsequently refined based on feedback from this process. One reviewer (YKK) extracted the data from the included articles while another reviewer (OW) verified the extracted data by cross-checking 10% of the full-text articles against the extracted data to ensure that the correct variables have been extracted. Critical appraisal of the quality of the included studies was deemed to be beyond the scope of this study and is not considered mandatory for scoping reviews [20].

Presentation and charting of results

We analysed the extracted data descriptively and results are presented using tables, charts, and maps to ensure adequate visualisation of the key findings. We presented the number of studies published per country from 1978–2021 using a thematic map. The determinants of timeliness of routine childhood vaccination are organised according to *a priori* categories adapted from the 3-delays conceptual framework [21]. *Delay-1* relates to decision to seek care and includes factors such as household socioeconomic and cultural characteristics; *Delay-2* relates to arrival at a health facility and includes factors such as geographic accessibility and transportation; *Delay-3* are factors related to provision of adequate care at facility level [21]. We categorised the included studies to determine if censored data was accounted for during data analysis. Studies that statistically adjusted for children yet to be vaccinated at the time of the empiric studies are considered to have accounted for *right censoring*. On the other hand, studies that statistically adjusted for children vaccinated before data collection but without precise vaccination records are considered to have accounted for *left censoring*.

Role of the funding source

The funder of the research had no role in the design, selection, data collection, data analysis, data interpretation, or writing of the report of this scoping review.

Results

A total of 6 819 publications were identified (Fig 1). After duplicate removal, 4263 records were eligible for screening. After screening these records by title and abstract, 260 publications

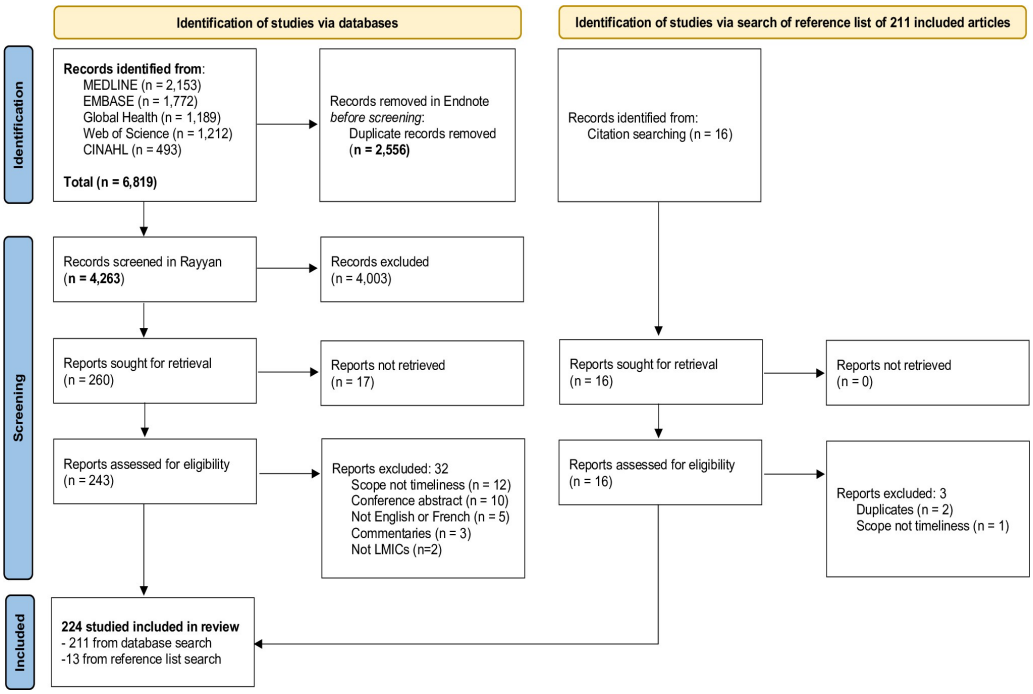


Fig 1. Flowchart showing study identification, screening, and selection process.

https://doi.org/10.1371/journal.pgph.0000325.g001

were selected for full-text screening; however, full-texts were not available for 17 titles even after contacting their authors as these articles were not open access. We further excluded 32 articles, leaving 211 articles for inclusion and 13 additional articles that fulfilled the inclusion criteria were identified from a search of the reference lists of the 211. Overall, 224 studies were included for analysis of which 13 were multi-country studies with the remaining 211 being single country reports. (S2 and S3 Tables).

Over one-third (35%; 78/224) of published studies were from the WHO African region, with only 2% (6/224) and 6% (15/224) from the European and America Region, respectively (Fig 2B). The included studies represented 103 of the 137 LMIC studied (S1 Table and S1 Checklist) with China (WHO Western Pacific Region; 40 articles), India (WHO South-East Asia Region; 27 articles), and Kenya (WHO African Region; 23 articles) being most represented countries (Fig 3).

The earliest reported study exploring timeliness of routine childhood vaccination in LMICs was published in 1987 [23]. Since 2004, we observed a gradual increase in relevant publications with the most rapid increase from 2013, with 20 articles already published in the first six months of 2021 (Fig 2A). The most common vaccines that have been the focus of studies on the timeliness of routine childhood are DTP3/Penta3 and MCV1 with 137 articles each. The least studied antigen was the yellow fever vaccine while the second doses of multi-dose vaccines were generally less studied (Fig 2C).

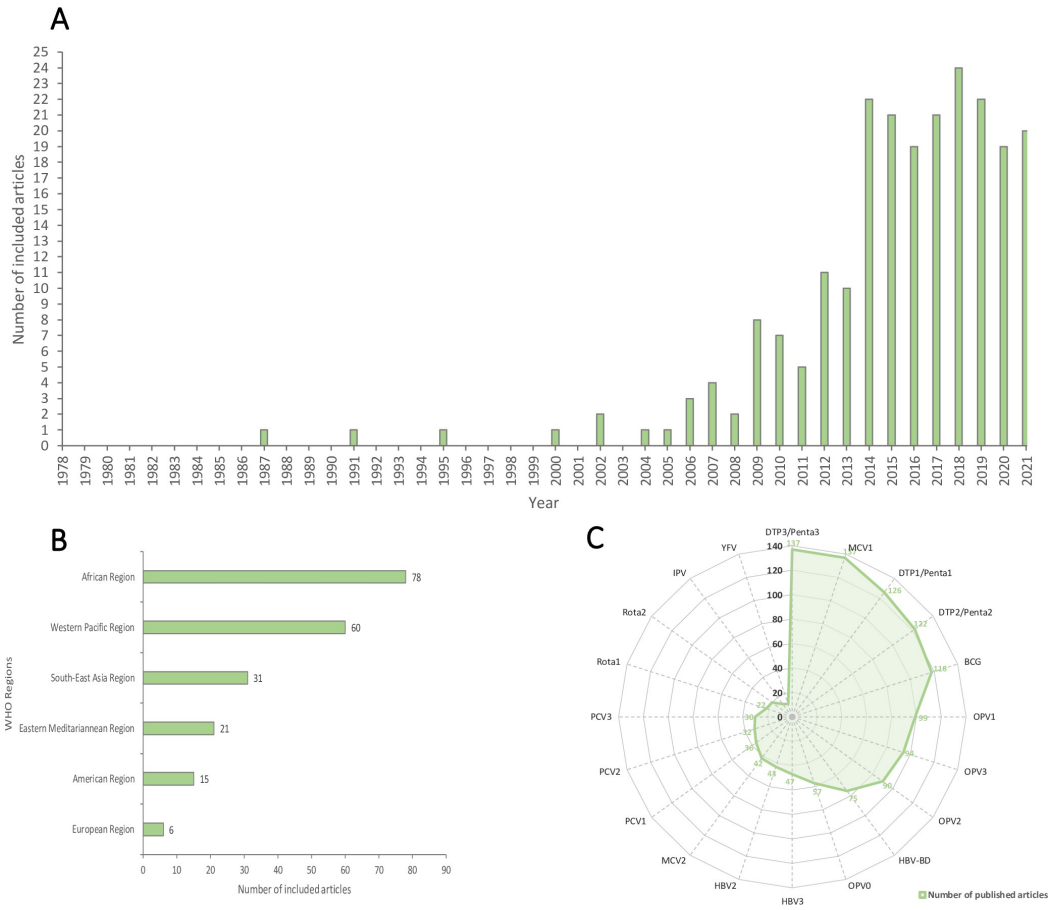


Fig 2. (a) How the literature on the timeliness of routine childhood vaccination has evolved, 1978–2021 Number of studies published per year (b) number of studies published per WHO region (c) antigens studied in the published literature.

https://doi.org/10.1371/journal.pgph.0000325.g002

Domains and definitions of vaccination timeliness

All included studies but one [99.5% (223/224)] [24] explored the timeliness domain of 'delayed vaccination'. Less frequently studied were 'early vaccination' (receipt of a vaccine before the recommended schedule; 21.9% (49/224) of studies) and 'untimely interval vaccination' (receipt of a subsequent dose of a multi-dose antigen outside the recommended EPI window; 9% (20/224) of studies) (Fig 4A). We observed varying cut-off values for defining 'untimely interval', 'early', or 'delayed' vaccination. Among studies exploring 'untimely interval vaccination', four different definitions were used but over half [55% (11/20)] of the studies considered 4 weeks beyond the accepted EPI interval as being untimely (Fig 4B). Among the 49 studies that focused on 'early vaccination', seven different definitions were used, with the most used definition [63% (31/49)] being 'any time before the accepted EPI schedule' (Fig 4C). With 19

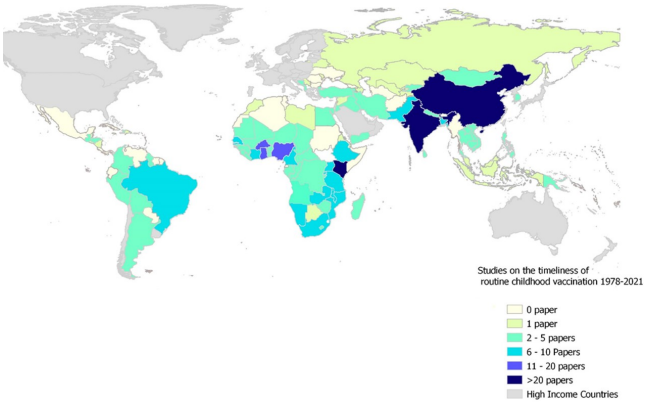


Fig 3. Map of the world showing low-and middle-income countries where studies on the timeliness of routine childhood vaccination has been conducted, 1978–2021. This map was produced by the authors with administrative boundaries data from geoBoundaries [22].

https://doi.org/10.1371/journal.pgph.0000325.g003

different definitions, delayed vaccination had the highest number of definitions of the domains studied (Table 1). Specifically, delayed birth-dose of hepatitis-B vaccine was defined in 15 different ways (Fig 4D).

Operationalisation of vaccination timeliness

Untimely interval, early, and delayed vaccination were measured or operationalised in various ways by the included studies (Fig 4A). Most studies [72.3% (166/224)] operationalised untimely interval, early, and delayed vaccination as categorical measures such as the proportion of the study population with the different domains of vaccination timeliness using the operational definitions. However, only 9.8% (22/224) of studies operationalised these domains using continuous measures such as median and mean delay or early vaccinations (Fig 4A).

Methodological and statistical gaps

During data collection for the included studies, the majority [47.8% (107/224)] excluded the data of children whose caregivers had no vaccination cards or written records of their vaccination irrespective of caregivers' recall of their vaccination status (Table 2). In 9.4% (21/224) of studies, it was not clear how scenarios where vaccination records were not available for some children was handled by the authors.

The majority [76.3% (171/224)] of studies did not account for any form of censored event [i.e., a child being vaccinated before their study but without a record (*left censoring*) or vaccination that would occur outside their study period (*right censoring*)]. There were 50 studies (22.3%) that accounted only for right censored data—i.e., children who were not vaccinated as of the time of the study but with a possibility of being vaccinated afterwards. Most of these studies used survival analysis techniques such as Kaplan-Meier statistics. Only three studies [98, 109, 147] accounted for both right and left censoring using survival analysis approach such as Turnbull and Weibull statistics (Table 2).

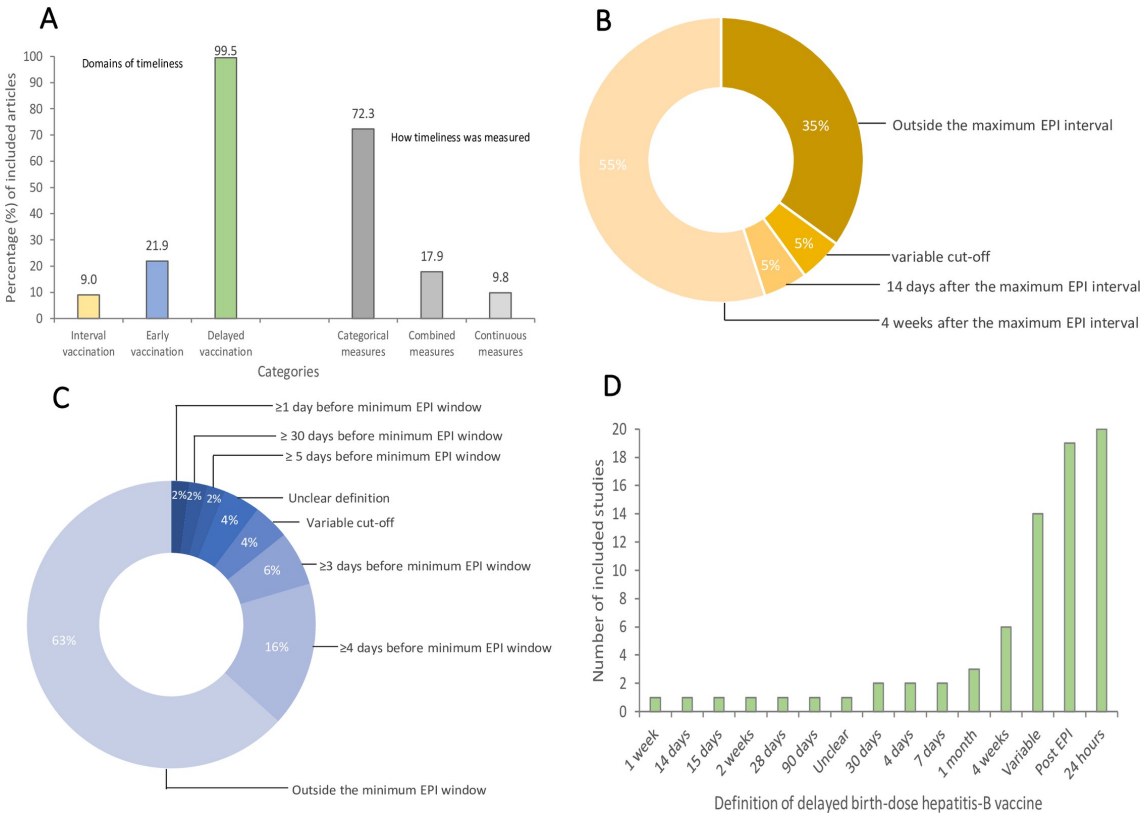


Fig 4. How the timeliness of routine childhood vaccination was defined and measured in the literature, 1978–2021 (a) domains of timeliness explored and how timeliness was operationalised (b) how untimely interval vaccination was defined (c) how early vaccination was defined (d) how delayed birth-dose hepatitis-B vaccine (HBV-BD) was defined. Note, in Fig 4D, the definition timelines are relative to the day of birth.

https://doi.org/10.1371/journal.pgph.0000325.g004

Determinants of vaccine timeliness

Over two-thirds [68.3%; 153/224] of studies discussed factors associated with socioeconomic and household-level determinants (Delay 1) specifically, maternal education (46.4%); child's sex (35.3%); family wealth (33%); place of residence (29.5%); maternal age (27.2%); child's place of birth (25%); and maternal occupation (20.1%). Factors associated with accessibility of health facilities or immunisation clinics (Delay 2) were the least explored, accounting for 15.6% (35/224) of studies (Fig 5). Among the Delay 2 factors, reported travel distance was the most explored in the literature [35, 47, 59, 61, 65, 68, 77–79, 87, 116, 119, 131, 165, 168, 182, 203, 206, 217, 222, 223, 234, 235, 242]. Broader determinants such as conflict/humanitarian crises, and large public health crises such as COVID-19 which fall outside the traditional 3-delay categories, have been rarely studied. So far, only one published study has explored the impact of the ongoing COVID-19 pandemic on the timeliness of receiving routine childhood vaccination over an 18-month period following the onset of the pandemic (i.e., January 2020 – July 2021) [132].

Table 1. How delayed routine childhood vaccination was defined in the 223 studies from LMICs that focused on this domain of timeliness, 1978–2021.

Studies	Cut-off or definition used	Definition of delayed vaccination
[25–47]	24 hours	Hepatitis B vaccine birth doses received after 24 hours of birth
[48–50]	4 days	EPI vaccine doses received ≥4 days after the recommended age of vaccination
[51–56]	1 week or 7 days	EPI vaccine doses received 1 week or 7 days after the scheduled or recommended age of vaccination
[57–61]	14 days or 2 weeks	EPI vaccine doses received 14 days or 2 weeks after the scheduled or recommended age of vaccination
[62]	15 days	EPI vaccine doses received 15 days after the scheduled or recommended age of vaccination
[63–95]	28 days or 4 weeks	EPI vaccine doses received 28 days or 4 weeks after the scheduled or recommended age of vaccination
[96]	29 days	EPI vaccine doses received 29 days after the recommended age of vaccination
[97–106]	30 days	EPI vaccine doses received 30 days after the recommended age of vaccination
[107, 108]	30.5 days	EPI vaccine doses received 30.5 days after the recommended age of vaccination
[109]	32 days	EPI vaccine doses received 32 days after the recommended age of vaccination
[110–121]	1 month	EPI vaccine doses received 1 month after the scheduled or recommended age of vaccination
[122]	2 months	EPI vaccine doses received 2 months after the recommended age of vaccination
[123]	60 days	EPI vaccine doses received 60 days after the recommended age of vaccination
[124]	90 days	EPI vaccine doses received 90 days after the recommended age of vaccination
[125]	>12 months of life	EPI vaccine doses received after 12 months of life
[23, 126–202]	Outside EPI window*	EPI vaccine doses received outside the country-specific EPI or WHO recommended vaccination windows
[203–205]	Outside manufacturer's recommended window	EPI vaccine doses received outside the manufacturer's recommended vaccination windows
[206–211]	Unclear cut-off**	Although delayed vaccination was studied, there was no clear definition or cut-off value
[212–245]	Variable cut-off***	Several cut-offs used in the same study to define delayed vaccination of the same or different antigens in the schedule

*These relied on the national EPI window in the country of the study. Any vaccine received outside the maximum date of the window was considered delayed.

**These studies focused on the domain 'delayed vaccination', however, did not explicitly document what operational definition was used.

***These studies measured delayed vaccination using multiple or variable definitions and reported multiple estimates for delayed vaccination.

https://doi.org/10.1371/journal.pgph.0000325.t001

Discussion

Our scoping review show that 'delayed vaccination' was the commonest domain of vaccination timeliness studied, however, there were varying definitions for early, untimely interval, and delayed vaccination even in studies from the same country or focused on same vaccine. Most of the studies operationalised vaccination timeliness as a categorical variable. There was a lack of uniformity in handling situations where children were already vaccinated but lacked

Table 2. Analytic and statistical gaps in the 224 included studies on the timeliness of routine childhood vaccination, 1978–2021.

Variable	Number of articles (N = 224)	Proportion (%)
Statistically accounting for censored data		
Not done	171	76.3
Right censoring only	50	22.3
Both Right and Left censoring	3	1.4
Unavailable precise vaccination records		
Excluded data	107	47.8
Not applicable*	75	33.5
Unclear	21	9.4
Included data	21	9.4

*These studies were based on data from health information management systems (HIMS) or facility-based records, hence, vaccination dates were available.

https://doi.org/10.1371/journal.pgph.0000325.t002

information on precise vaccination dates. Demand-side factors such as socioeconomic and cultural determinants were most commonly studied, while supply-side or broader determinants such as factors related to accessibility of immunisation service points were the least studied determinants.

Vaccination schedules are designed with age-specific immunity and risks of disease in mind, thus, they target the best possible points of early childhood to ensure children develop

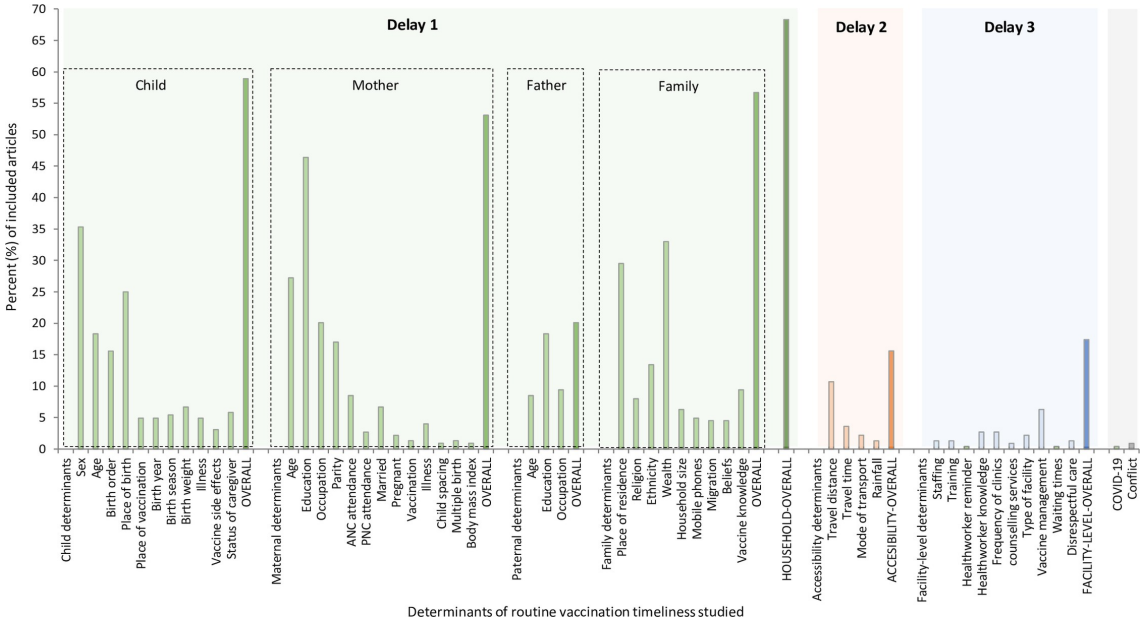


Fig 5. Determinants of the timeliness of routine childhood vaccination studied in low-and middle-income countries, 1978–2021. Note: Delay 1, 2, and 3 are based on the 3-delay conceptual framework developed by Thaddeus and Maine [21].

https://doi.org/10.1371/journal.pgph.0000325.g005

adequate immunity against VPDs as early as possible [7]. Furthermore, the intervals for multi-dose antigens is aimed at optimising immune responses against VPDs [5]. The vaccination schedules in early infancy, therefore, leaves little room for vaccination to be given before their due dates or delayed significantly. Although there are recommendation from the WHO regarding vaccination schedules, country-level vaccination windows are designed, taking into consideration, the local disease epidemiology, availability of resources, programmatic and policy considerations. Thus, the recommended age of vaccination for a specific vaccine in some LMICs might differ slightly from those in other countries. The lack of comparable definitions for early, untimely interval, and delayed vaccination could be partly explained by these variations in accepted windows across LMICs. However, we found that even for antigens such as the birth-dose of hepatis-B vaccine that is recommended within the 1st 24 hours of life by the WHO, [246] there was no uniformity in the definitions used across studies. Irrespective of context, or antigen of focus, generating point estimates around each domain of vaccination timeliness through a meta-analysis to understand intra- or inter-country gaps in reaching antigen-specific targets will be limited due to the heterogeneity in the cut-off points used across studies.

An important measurement gap in the literature was that most studies operationalised the domains of vaccination timeliness as categorical variables. That is, most studies categorised doses as either 'on-time' if received within the cut-off points of the operational definition used, or as early, untimely interval, or delayed vaccination if received outside the specified operational definition, reported as proportions. While this approach appears pragmatic, it potentially lumps together a wide window of untimely vaccinations and obscures a nuanced interpretation of the data on vaccination timeliness. Unpacking and presenting the domains of vaccination timeliness as continuous variables, for example, as mean or median days delayed (outside the nationally accepted window) could be considered more robust. Clusters of children with a longer mean delay, potentially have a higher risk of VPDs exposure and likelihood of not completing their schedules compared to their counterparts with shorter delays. Additionally, comparatively longer untimely vaccination in a particular sub-national unit, potentially highlights equity gaps which must be bridged, or an early warning sign of weaknesses in immunisation programmes.

A key methodological gap was the lack of a uniform approach in handling censored data—i.e., situations where vaccination dates or time to vaccinations were not available for all participants. The commonest, in the included studies *left and right censoring*. Only three studies [98, 109, 147] accounted for both scenarios where precise vaccination dates were unavailable. Left censored data is common in LMICs where retention rates of vaccine cards are variable, and complete clinical records are seldom available. Using approaches that account for both right and left censoring improves the robustness of timeliness estimates, because it permits more observations (including those without vaccination records) to be included in the analysis that might otherwise have been excluded.

Factors related to the geographic accessibility of immunisation clinics, clinic-level and service delivery-related determinants have been less studied, compared to socioeconomic and cultural determinants of vaccination timeliness. This finding could have been due to the fact that data on geographic accessibility of health services is not routinely collected as part of health surveys, as this requires skilled personnel to collect and adequately model accessibility, compared to describing socioeconomic variables which are more routine. Nonetheless, there is evidence to suggest that geographic accessibility to immunization service points impacts the likelihood of receiving childhood vaccination in an age-appropriate manner [247, 248]. How remotely away from a clinic a family lives, how long they had to travel for an appointment,

geospatial relationships in catchment areas of clinics and the presence (or lack thereof) of accessible roads can all impact the uptake of health services, including vaccination.

There is no doubt that epidemics/pandemics, conflicts, and disasters such as earthquakes and flooding impact the delivery of health services, including timely receipt of vaccines. Since December 2019, an additional challenge has been posed by the ongoing COVID-19 pandemic, which has resulted in disruptions of immunisation systems [3, 249]. Despite the potential effect of the COVID-19 pandemic on routine vaccination timeliness, to date, only one study, [132] have explored the impact of the pandemic on vaccination timeliness. It is expected that the COVID-19 pandemic will continue to determine how timely children in many LMICs receive their vaccines, thus, future studies should explore its impact on vaccination timeliness. Understanding how, where, and to what extent fragile contexts impact the timeliness of receiving routine vaccination is an important initial step for EPI programmes to plan mitigating measures during such circumstances.

Our study has some limitations which must be considered. First, by including only studies published in English and French, we could have omitted a small number of studies published in other languages. Similarly, we did not include grey literature such as official government reports on vaccination timeliness. We also acknowledge that a handful of studies would have been published since our search was completed on 01 July 2021 as our study is not a 'living Review'. While a very small number of reports might have been published after we concluded our search, or might have been published in other languages and as grey literature, we do not expected them to significantly alter the conclusions drawn from our study which was based on 224 published articles, spanning 1978–2021. Second, we did not include studies that focused on vaccinations given outside the routine childhood EPI schedule, including those given in adolescence, and adulthood, for example maternal tetanus vaccinations. Third, although appraisal of study quality or design is primarily not the focus of scoping reviews, there was substantial variability in the quality and design of the included studies that potentially explains the observed measurement and methodological gaps. Despite these limitations, our study highlight important gaps related to the design, conduct and reporting of studies on vaccination timeliness that could shape future studies on this topic, and potentially improve their utility and comparability.

To date, this is the most extensive review spanning four decades aimed at understanding the measurement and methodological gaps in the literature on the timeliness of routine childhood vaccination in LMICs. To our knowledge, the first and only previous review on the subject by Masters et. al. (2019) [10] provided valuable insights into some existing measurement and methodological gaps in the literature on timeliness of vaccination; however, the review had key limitations that necessitated a further review. First, the review was limited to studies published between 2007–2017, and therefore did not include important studies published prior to 2007, or after 2017. Second, the review focused on three electronic databases and was restricted to studies published in English language only. Due to the extensive nature of our scoping review, we included 224 studies compared with only 67 in the review by Master et.al, thus, making our study more extensive.

Implications for future research, policy, and practice

Based on our findings, future studies on the timeliness of routine childhood vaccination should, at minimum, pay attention to the following methodological and measurement issues to ensure the robustness, comparability, and utility of their findings. First, to bridge the methodological gap related to lack of a comparable cut-off or definition of early, untimely interval, and delayed vaccination, future studies should consider defining vaccine doses received

outside the nationally accepted EPI vaccination windows in their countries as early, untimely interval, or delayed as was done by some studies. Second, operationalising untimely vaccination as a categorical variable prevents a nuanced interpretation of vaccination timeliness. Thus, future studies should unpack and present the domains of vaccination timeliness as continuous variables, for example, as mean or median days vaccination was early or delayed outside the nationally accepted window. Through this approach, one can more clearly compare not just the proportion of children with untimely vaccination, but also on average, how many days outside the national vaccination window children are vaccinated too early or delayed across antigens–an important indicator of the quality of an immunisation programme. Also, such continuous variables can be easily converted to categorical variables, which may be more suitable when analysing individual level data. Third, deploying methodological approaches that account for situations where precise vaccination dates are unavailable potentially improves the power of the individual studies, thus, generating more reliable and precise estimates. Future studies can apply the Turnbull estimator, Weibull method, [250] or machine learning techniques to account for both left and right censored data as was done by three of the included studies. Fourth, to gain a robust understanding of the complex factors determining the timely receipt of vaccines, future studies should not only explore demand-side factors such socioeconomic or cultural determinants, but also, supply-side determinants including geographic accessibility to clinics, and facility-level factors. Lastly, the WHO and national immunisation programmes should develop and implement guidelines for measuring vaccination timeliness based on the accepted vaccination windows. Through this approach, measurement gaps related to the lack of a uniform cut-off for defining vaccination timeliness can be bridged, thus, improving the comparability and utility of data across antigens and settings.

Supporting information

S1 Table. Full search strategy in MEDLINE (Ovid).
(DOCX)

S2 Table. Summary characteristics of included studies.
(DOCX)

S3 Table. List of 46 low-and middle-income countries that were not the focus of a single study but contributed data to the 13 studies that were based on multiple countries.
(DOCX)

S1 Checklist. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.
(DOCX)

Acknowledgments

We would like to acknowledge Russell Burke, Assistant Librarian, Library & Archives Service, at the London School of Hygiene and Tropical Medicine (LSHTM) for providing guidance during the development and refinement of the search strategy for this scoping review.

Author Contributions

Data curation: Oghenebrume Wariri, Yakubu Kevin Kwarshak.

Formal analysis: Oghenebrume Wariri.

Methodology: Oghenebrume Wariri, Uduak Okomo, Yakubu Kevin Kwarshak, Chigozie Edson Utazi, Kris Murray, Chris Grundy, Beate Kampmann.

Project administration: Oghenebrume Wariri.

Resources: Oghenebrume Wariri.

Supervision: Uduak Okomo, Chigozie Edson Utazi, Kris Murray, Chris Grundy, Beate Kampmann.

Visualization: Oghenebrume Wariri.

Writing – original draft: Oghenebrume Wariri, Uduak Okomo.

Writing – review & editing: Oghenebrume Wariri, Uduak Okomo, Yakubu Kevin Kwarshak, Chigozie Edson Utazi, Kris Murray, Chris Grundy, Beate Kampmann.

References

1. Keja K, Chan C, Hayden G, Henderson RH. Expanded programme on immunization. World Health Stat Q 1988; 41(2): 59–63. PMID: 3176515
2. World Health Organization. Immunization coverage. 2021. https://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage (accessed August 17 2021).
3. Causey K, Fullman N, Sorensen RJD, Galles NC, Zheng P, Aravkin A, et al. Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study. Lancet 2021; 398(10299): 522–34. https://doi.org/10.1016/S0140-6736(21)01337-4 PMID: 34273292
4. World Health Organization. Regional Office for the Western P. Routine immunization services during the COVID-19 pandemic. CC BY-NC-SA 3.0 IGO: Manila: WHO Regional Office for the Western Pacific, 2020.
5. World Health Organization. Training for mid-level managers (MLM) module 5: Monitoring the immunization system. Geneva: World Health Organization,.
6. Walton S, Cortina-Borja M, Dezateux C, Griffiths LJ, Tingay K, Akbari A, et al. Measuring the timeliness of childhood vaccinations: Using cohort data and routine health records to evaluate quality of immunisation services. Vaccine 2017; 35(51): 7166–73. https://doi.org/10.1016/j.vaccine.2017.10.085 PMID: 29132992
7. Plotkin SA. Vaccines: Past, present and future. Nature Medicine 2005; 11(4S): S5–S. https://doi.org/10.1038/nm1209 PMID: 15812490
8. Guerra FA. Delays in immunization have potentially serious health consequences. Paediatr Drugs; 2007. p. 143–8. https://doi.org/10.2165/00148581-200709030-00002 PMID: 17523694
9. Henderson DA, Dunston FJ, Fedson DS, Fulginiti VA, Gerety RJ, Guerra FA, et al. The Measles Epidemic: The Problems, Barriers, and Recommendations. JAMA 1991; 266(11): 1547–52. PMID: 1880887
10. Masters NB, Wagner AL, Boulton ML. Vaccination timeliness and delay in low- and middle-income countries: a systematic review of the literature, 2007–2017. Hum Vaccin Immunother. 2019; 15(12): 2790–805. https://doi.org/10.1080/21645515.2019.1616503 PMID: 31070992
11. GBD 2020 R, Vaccine Coverage Collaborators. Measuring routine childhood vaccination coverage in 204 countries and territories, 1980–2019: a systematic analysis for the Global Burden of Disease Study 2020, Release 1. Lancet 2021; 398(10299): 503–21. https://doi.org/10.1016/S0140-6736(21)00984-3 PMID: 34273291
12. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. 2018; 18(1): 143. https://doi.org/10.1186/s12874-018-0611-x PMID: 30453902
13. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology 2005; 8(1): 19–32.
14. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth 2020; 18(10): 2119–26. https://doi.org/10.11124/JBIES-20-00167 PMID: 33038124

15. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018; 169(7): 467–73. https://doi.org/10.7326/M18-0850 PMID: 30178033

16. Wariri O, Okomo U, Kwarshak YK, Murray KA, Grundy C, Kampmann B. Timeliness of routine childhood vaccination in low- and middle-income countries, 1978–2021: Protocol for a scoping review to map methodologic gaps and determinants. PLoS One 2021; 16(6): e0253423. https://doi.org/10.1371/journal.pone.0253423 PMID: 34138965

17. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. JBI Evidence Implementation 2015; 13(3). https://doi.org/10.1097/XEB.0000000000000050 PMID: 26134548

18. The World Bank. World Bank Country and Lending Groups. 2020. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed April 12 2021).

19. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016; 5(1): 210. https://doi.org/10.1186/s13643-016-0384-4 PMID: 27919275

20. Joanna Briggs Institute. Data extraction. JBI's Reviewers Manual for Evidence Synthesis. 2019. https://wiki.jbi.global/display/MANUAL/11.2.7+Data+extraction (accessed March 17 2021).

21. Thaddeus S, Maine D. Too far to walk: Maternal mortality in context. Soc Sci Med. 1994; 38(8): 1091–110. https://doi.org/10.1016/0277-9536(94)90226-7 PMID: 8042057

22. Runfola D, Anderson A, Baier H, Crittenden M, Dowker E, Fuhrig S, et al. geoBoundaries: A global database of political administrative boundaries. PLoS One 2020; 15(4): e0231866. https://doi.org/10.1371/journal.pone.0231866 PMID: 32330167

23. Ferrinho P, Gear JS, Reinach SG. Some aspects of vaccination coverage in the Gelukspan health ward. S Afr Med J. 1987; 72(5): 341–2. PMID: 3616841

24. Cutts FT, Zell ER, Soares AC, Diallo S. Obstacles to achieving immunization for all 2000: missed immunization opportunities and inappropriately timed immunization. J Trop Pediatr. 1991; 37(4): 153–8. https://doi.org/10.1093/tropej/37.4.153 PMID: 1960770

25. Danjuma SD, Ibrahim AI, Shehu NY, Diala MU, Pam CV, Ogbodo CO. At-birth vaccination timeliness: An analysis of inborns in the highlands of Jos, North-Central Nigeria. Niger Postgrad Med J.2020; 27 (3): 209–14. https://doi.org/10.4103/npmj.npmj_44_20 PMID: 32687121

26. Ork V, Woodring J, Hossain MS, Wasley A, Nagashima S, Yamamoto C,et al. Hepatitis B surface antigen seroprevalence among pre- and post-vaccine cohorts in Cambodia, 2017. Vaccine 2019; 37(35): 5059–66. https://doi.org/10.1016/j.vaccine.2019.06.073 PMID: 31285088

27. Moturi E, Tevi-Benissan C, Hagan JE, Shendale S, Mayenga D, Murokora D, et al. Implementing a Birth Dose of Hepatitis B Vaccine in Africa: Findings from Assessments in 5 Countries. J Immunol Sci. 2018; (5): 31–40. PMID: 30931434

28. Lopez AL, Ylade M, Daag JV, Tandoc AO 3rd, Bonifacio J, Sylim PG, et al. Hepatitis B seroprevalence among 5 to 6 years old children in the Philippines born prior to routine hepatitis B vaccination at birth. Hum Vaccin Immunother. s 2018; 14(10): 2491–6. https://doi.org/10.1080/21645515.2018.1480278 PMID: 29852077

29. Liu X, Yang C, Zhong Q, Huang X, Yang Y, Huang Y, et al. Improved timely birth dose coverage of hepatitis B vaccine narrows the socio-economic inequality in western China in 2011–2016. Vaccine 2018; 36(27): 3901–7. https://doi.org/10.1016/j.vaccine.2018.05.085 PMID: 29844000

30. Hu Y, Chen Y, Wang Y, Liang H. Hepatitis B Vaccination among 1999–2017 Birth Cohorts in Zhejiang Province: The Determinants Associated with Infant Coverage. Int J Environ Res Public Health. 2018; 15(12).

31. Wu J, Li D, Zhou Y, Du M, Piao H. Relationship between receipt of substitutable for-fee vaccines and completion of the expanded programme on immunisation: a cross-sectional study in Fujian, China. BMJ Open 2017; 7(7): e015666. https://doi.org/10.1136/bmjopen-2016-015666 PMID: 28729316

32. Li X, Heffelfinger J, Wiesen E, Diorditsa S, Valiakolleri J, Nikuata AB, et al. Improving hepatitis B birth dose coverage through village health volunteer training and pregnant women education. Vaccine 2017; 35(34): 4396–401. https://doi.org/10.1016/j.vaccine.2017.06.056 PMID: 28688784

33. Wu J, Li D, Zhou Y. Association between timely initiation of hepatitis B vaccine and completion of the hepatitis B vaccine and national immunization program vaccine series. Int J Infect Dis. 2016; 51: 62–5. https://doi.org/10.1016/j.ijid.2016.08.018 PMID: 27592194

34. Wiesen E, Lagani W, Sui G, Arava J, Reza S, Diorditsa S, et al. Assessment of the hepatitis B birth dose vaccination program, Papua New Guinea, 2014. Vaccine 2016; 34(3): 367–72. https://doi.org/10.1016/j.vaccine.2015.11.044 PMID: 26620839

35. Miyahara R, Jasseh M, Gomez P, Shimakawa Y, Greenwood B, Keita K, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. Vaccine 2016; 34(29): 3335–41. https://doi.org/10.1016/j.vaccine.2016.05.017 PMID: 27195759

36. Wu JN, Wen XZ, Zhou Y, Lin D, Zhang SY, Yan YS. Impact of the free-vaccine policy on timely initiation and completion of hepatitis B vaccination in Fujian, China. J Viral Hepat. 2015; 22(6): 551–60. https://doi.org/10.1111/jvh.12359 PMID: 25377649

37. Mutua MK, Ochako R, Ettarh R, Ravn H, Echoka E, Mwaniki P. Effects of low birth weight on time to BCG vaccination in an urban poor settlement in Nairobi, Kenya: an observational cohort study. BMC pediatr 2015; 15: 45. https://doi.org/10.1186/s12887-015-0360-5 PMID: 25903935

38. Sadoh AE, Ofili A. Hepatitis B infection among Nigerian children admitted to a children's emergency room. Afr Health Sci. s 2014; 14(2): 377–83. https://doi.org/10.4314/ahs.v14i2.13 PMID: 25320587

39. Patel MK, Capeding RZ, Ducusin JU, Castro MD, Garcia LC, Hennessey K. Findings from a hepatitis B birth dose assessment in health facilities in the Philippines: Opportunities to engage the private sector. Vaccine 2014; 32(39): 5140–4. https://doi.org/10.1016/j.vaccine.2013.11.097 PMID: 24361121

40. Sadoh AE, Sadoh WE, Uduebor J, Ekpebe P, Iguodala O. Factors contributing to delay in commencement of immunisation in Nigerian infants. Tanzan J Health Res. 2013; 15(3): 186–92. https://doi.org/10.4314/thrb.v15i3.6 PMID: 26591708

41. Hutin Y, Hennessey K, Cairns L, Zhang Y, Li H, Zhao L, et al. Improving hepatitis B vaccine timely birth dose coverage: lessons from five demonstration projects in China, 2005–2009. Vaccine 2013; 31: J49–55. https://doi.org/10.1016/j.vaccine.2013.03.025 PMID: 24331021

42. Xiao J, Zhang J, Wu C, Shao X, Peng G, Peng Z, et al. Impact of hepatitis B vaccination among children in Guangdong Province, China. Int J Infect Dis. 2012; 16(9): e692–6. https://doi.org/10.1016/j.ijid.2012.05.1027 PMID: 22795176

43. Cui FQ, Li L, Hadler SC, Wang F, Zheng H, Chen Y, et al. Reprint of: Factors associated with effectiveness of the first dose of hepatitis B vaccine in China: 1992–2005. Vaccine 2010; 31: J56–J61.

44. Zhou Y, Wang H, Zheng J, Zhu X, Xia W, Hipgrave DB. Coverage of and influences on timely administration of hepatitis B vaccine birth dose in remote rural areas of the People's Republic of China. Am J Trop Med Hyg. 2009; 81(5): 869–74. https://doi.org/10.4269/ajtmh.2009.09-0238 PMID: 19861624

45. Wang L, Li J, Chen H, Li F, Armstrong GL, Nelson C, et al. Hepatitis B vaccination of newborn infants in rural China: evaluation of a village-based, out-of-cold-chain delivery strategy. Bull World Health Organ. 2007; 85(9): 688–94. https://doi.org/10.2471/blt.06.037002 PMID: 18026625

46. Choconta-Piraquive LA, De la Hoz-Restrepo F, Sarmiento-Limas CA. Compliance with birth dose of Hepatitis B vaccine in high endemic and hard to reach areas in the Colombian amazon: results from a vaccination survey. BMC Health Serv Res. 2016; 16: 293. https://doi.org/10.1186/s12913-016-1542-z PMID: 27443313

47. Périères L, Marcellin F, Lo G, Protopopescu C, Ba EH, Coste M, et al. Hepatitis B Vaccination in Senegalese Children: Coverage, Timeliness, and Sociodemographic Determinants of Non-Adherence to Immunisation Schedules (ANRS 12356 AmBASS Survey). Vaccines (Basel) 2021; 9(5).

48. Janusz CB, Frye M, Mutua MK, Wagner AL, Banerjee M, Boulton ML. Vaccine Delay and Its Association With Undervaccination in Children in Sub-Saharan Africa. Am J Prev Med. 2021; 60(1): S53–S64. https://doi.org/10.1016/j.amepre.2020.10.003 PMID: 33189500

49. Wambui EW, Keraka M, Nguhiu P. The role of maternal, psychosocial and social-cultural factors in HIV-Exposed Infants' service uptake; Nakuru County Referral Hospital, Kenya. East African Medical Journal 2017; 94(12): 1010–27.

50. Edstam JS, Dulmaa N, Nymadawa P, Rinchin A, Khulan J, Kimball AM. Comparison of hepatitis B vaccine coverage and effectiveness among urban and rural mongolian 2-year-olds. Prev Med. 2002; 34 (2): 207–14. https://doi.org/10.1006/pmed.2001.0972 PMID: 11817916

51. Ateudjieu J, Yakum MN, Goura AP, Tembei AM, Ingrid DK, Bita'a Landry B, et al. EPI immunization coverage, timeliness and dropout rate among children in a West Cameroon health district: a cross sectional study. BMC public health 2020; 20(1): 228. https://doi.org/10.1186/s12889-020-8340-6 PMID: 32054484

52. Tooke L, Louw B. A successful preterm vaccination program in a neonatal unit in a developing country. Heliyon 2019; 5(11): e02857. https://doi.org/10.1016/j.heliyon.2019.e02857 PMID: 31844744

53. Subbiah P RA, Chavada VK, Vasudevan KP. A retrospective study on timeliness of vaccination among children aged 0 to 23 months in a rural area of Pondicherry. International Journal Of Community Medicine And Public Health 2019; 6: 2127–32.

54. Pindyck T, Tate JE, Bonkoungou IJO, Armah G, Mujuru HA, Rugambwa C, et al. Timeliness of rotavirus vaccination at sentinel sites in four early-adopter African countries. Vaccine 2019; 37(40): 6002–7. https://doi.org/10.1016/j.vaccine.2019.08.008 PMID: 31455587

55. Abidin ZZ., Juni MH., Ibrahim F. Adherence towards Different Vaccines of Childhood Immunization of Under Five Year Old Children. Malaysian Journal of Medicine and Health Sciences 2017; 13(3): 61–9.

56. Holambe VM, Thakur NA. Correlates of delayed immunization: a cross sectional study at a tertiary care centre of Maharashtra, India. National Journal of Community Medicine 2013; 4(4): 621–3.

57. Hoest C, Seidman JC, Lee G, Platts-Mills JA, Ali A, Olortegui MP, et al. Vaccine coverage and adherence to EPI schedules in eight resource poor settings in the MAL-ED cohort study. Vaccine 2017; 35 (3): 443–51. https://doi.org/10.1016/j.vaccine.2016.11.075 PMID: 27998640

58. Gibson DG, Ochieng B, Kagucia EW, Were J, Hayford K, Moulton LH, et al. Mobile phone-delivered reminders and incentives to improve childhood immunisation coverage and timeliness in Kenya (M-SIMU): a cluster randomised controlled trial. Lancet Glob health. 2017; 5(4): e428–e38. https://doi.org/10.1016/S2214-109X(17)30072-4 PMID: 28288747

59. Chiabi A, Nguefack FD, Njapndounke F, Kobela M, Kenfack K, Nguefack S, et al. Vaccination of infants aged 0 to 11 months at the Yaounde Gynaeco-obstetric and pediatric hospital in Cameroon: how complete and how timely? BMC pediatr 2017; 17(1): 206. https://doi.org/10.1186/s12887-017-0954-1 PMID: 29258463

60. Ramaswamy G., Pruthu TK, Selvaraj K, Vinayagamurthy VM, Chinnakali P. Timeliness of primary childhood vaccination in a rural area of Puducherry, South India: evidence from routine management information system. International Journal of Contemporary Pediatrics 2014; 1(3): 131–4.

61. Banwat M.E., Bupwatda P.W., Lar L.A., Apagu A.A., A.I. Z. Effect of peer education on timeliness and completeness of routine immunization: An assessment in rural communities in North-Central Nigeria. International Journal of Community Research 2014; 3(3): 60–7.

62. Rauniyar SK, Munkhbat E, Ueda P, Yoneoka D, Shibuya K, Nomura S. Timeliness of routine vaccination among children and determinants associated with age-appropriate vaccination in Mongolia. Heliyon 2020; 6(9): e04898. https://doi.org/10.1016/j.heliyon.2020.e04898 PMID: 32995607

63. Raguindin PF, Morales-Dizon M, Aldaba J, Mangulabnan LP, Reyes RP, Batmunkh N, et al. Timeliness of childhood vaccinations in the Philippines. J Public Health Policy. 2021; 42(1): 53–70. https://doi.org/10.1057/s41271-020-00255-w PMID: 33398056

64. Mutua MK, Mohamed SF, Porth JM, Faye CM. Inequities in On-Time Childhood Vaccination: Evidence From Sub-Saharan Africa. Am J Prev Med. 2021; 60(1): S11–S23. https://doi.org/10.1016/j.amepre.2020.10.002 PMID: 33191062

65. Mekonnen ZA, Gelaye KA, Were M, Tilahun B. Effect of Mobile Phone Text Message Reminders on the Completion and Timely Receipt of Routine Childhood Vaccinations: Superiority Randomized Controlled Trial in Northwest Ethiopia. JMIR Mhealth Uhealth 2021; 9(6): e27603. https://doi.org/10.2196/27603 PMID: 34128813

66. Jones FK, Mensah K, Heraud J-M, Randriatsarafara FM, Metcalf CJE, Wesolowski A. The Challenge of Achieving Immunity Through Multiple-Dose Vaccines in Madagascar. Am J Epidemiol. 2021; 190 (10):2085–2093. https://doi.org/10.1093/aje/kwab145 PMID: 34023892

67. Alam MJ, Afsar MNA, Khanam A, Ahmad SM. Risk factors for delay in starting age-appropriate vaccinations among infants in urban slums of Bangladesh. Hum Vaccin Immunother. 2021; 17(9): 3186–91. https://doi.org/10.1080/21645515.2021.1908795 PMID: 34085905

68. Vasudevan L, Baumgartner JN, Moses S, Ngadaya E, Mfinanga SG. Parental concerns and uptake of childhood vaccines in rural Tanzania—a mixed methods study. BMC Public Health 2020; 20(1573). https://doi.org/10.1186/s12889-020-09598-1 PMID: 33081744

69. Mekonnen ZA, Gelaye KA, Were MC, Tilahun B. Timely completion of vaccination and its determinants among children in northwest, Ethiopia: a multilevel analysis. BMC public health 2020; 20(1): 908. https://doi.org/10.1186/s12889-020-08935-8 PMID: 32527248

70. Hefele L, Syphan S, Xayavong D, Homsana A, Kleine D, Chanthavilay P, et al. Timeliness of immunisation with the pentavalent vaccine at different levels of the health care system in the Lao People's Democratic Republic: A cross-sectional study. PloS one 2020; 15(12): e0242502. https://doi.org/10.1371/journal.pone.0242502 PMID: 33290386

71. Gunning CE, Mwanany a L, MacLeod WB, Mwale M, Thea DM, et al. Implementation and adherence of routine pertussis vaccination (DTP) in a low-resource urban birth cohort. BMJ open 2020; 10(12): e041198. https://doi.org/10.1136/bmjopen-2020-041198 PMID: 33384391

72. Agopian A, Young H, Quinlan S, Rice MM. Timeliness of childhood vaccinations in Armenia, 2015–2016. Vaccine 2020; 38(30): 4671–8. https://doi.org/10.1016/j.vaccine.2020.05.032 PMID: 32448619

73. Nalley JC., Maduka O. Completeness and timeliness of immunization among children aged 12 to 23 months in South-South Nigeria. Journal of Community Medicine and Primary Health Care 2019; 31 (1): 22–31.

74. Choudhary TS, Reddy NS, Aditi A, Sinha B, Roy S, Nair NP, et al. Delayed vaccination and its predictors among children under 2 years in India: insights from the National Family Health Survey-4. Vaccine 2019; 37(17): 2331–9. https://doi.org/10.1016/j.vaccine.2019.03.039 PMID: 30914221

75. Alrowaili GZR, Dar UF, y AH. May we improve vaccine timeliness among children? A cross sectional survey in Northern Saudi Arabia. J Family Community Med.2019; 26(2): 113–7. https://doi.org/10.4103/jfcm.JFCM_153_18 PMID: 31143083

76. Masters NB, Wagner AL, Carlson BF, Boulton ML. Vaccination timeliness and co-administration among Kenyan children. Vaccine 2018; 36(11): 1353–60. https://doi.org/10.1016/j.vaccine.2018.02.001 PMID: 29429814

77. Marban-Castro E, Sacoor C, Nhacolo A, Augusto O, Jamisse E, López-Varela E, et al. BCG vaccination in southern rural Mozambique: an overview of coverage and its determinants based on data from the demographic and health surveillance system in the district of Manhica. BMC pediatr. 2018; 18(1): 56. https://doi.org/10.1186/s12887-018-1003-4 PMID: 29439702

78. Hu Y, Chen Y, Liang H, Wang Y. An Overview of Coverage of BCG Vaccination and Its Determinants Based on Data from the Coverage Survey in Zhejiang Province. Int J Environ Res Public Health. 2018; 15(6). https://doi.org/10.3390/ijerph15061155 PMID: 29865207

79. Adetifa IMO, Karia B, Mutuku A, Bwanaali T, Makumi A, Wafula J, et al. Coverage and timeliness of vaccination and the validity of routine estimates: Insights from a vaccine registry in Kenya. Vaccine 2018; 36(52): 7965–74. https://doi.org/10.1016/j.vaccine.2018.11.005 PMID: 30416017

80. Upadhyay RP, Chowdhury R, Mazumder S, Taneja S, Sinha B, Martines J, et al. Immunization practices in low birth weight infants from rural Haryana, India: Findings from secondary data analysis. J Glob Health. 2017; 7(2): 020415. https://doi.org/10.7189/jogh.07.020415 PMID: 29423177

81. Schweitzer A, Akmatov MK, Krause G. Hepatitis B vaccination timing: results from demographic health surveys in 47 countries. Bull World Health Organ. 2017; 95(3): 199–209G. https://doi.org/10.2471/BLT.16.178822 PMID: 28250533

82. Sahoo DP, Jadhao AR, Deshmukh JS, Tekam AV, Raut RU. Timeliness of childhood vaccine uptake among children attending immunoprophylaxis clinic in central India. Journal of Evolution of Medical and Dental Sciences 2017; 6(73): 5232–7.

83. Mbengue MAS, Mboup A, Ly ID, Faye A, Camara FBN, Thiam M, et al. Vaccination coverage and immunization timeliness among children aged 12–23 months in Senegal: a Kaplan-Meier and Cox regression analysis approach. Pan Afr Med J. 2017; 27: 8. https://doi.org/10.11604/pamj.supp.2017.27.3.11534 PMID: 29296143

84. Zhou Y, Xing Y, Liang X, Yue C, Zhu X, Hipgrave D. Household survey analysis of the impact of comprehensive strategies to improve the expanded programme on immunisation at the county level in western China, 2006 2010. BMJ Open 2016; 6(3): e008663. https://doi.org/10.1136/bmjopen-2015-008663 PMID: 26966053

85. D'Ardenne KK, Darrow J, Furniss A, Chavez C, Hernandez H, Berman S, et al. Use of rapid needs assessment as a tool to identify vaccination delays in Guatemala and Peru. Vaccine 2016; 34(14): 1719–25. https://doi.org/10.1016/j.vaccine.2016.01.060 PMID: 26902545

86. Schweitzer A, Krause G, Pessler F, Akmatov MK. Improved coverage and timing of childhood vaccinations in two post-Soviet countries, Armenia and Kyrgyzstan. BMC public health 2015; 15: 798. https://doi.org/10.1186/s12889-015-2091-9 PMID: 26285702

87. Gibson DG, Ochieng B, Kagucia EW, Obor D, Odhiambo F, O'Brien KL, et al. Individual level determinants for not receiving immunization, receiving immunization with delay, and being severely underimmunized among rural western Kenyan children. Vaccine 2015; 33(48): 6778–85. https://doi.org/10.1016/j.vaccine.2015.10.021 PMID: 26482146

88. Zaidi SMA, Khowaja S, Dharma VK, Khan AJ, Ch, ir S. Coverage, timeliness, and determinants of immunization completion in Pakistan: Evidence from the Demographic and Health Survey (2006–07). Hum Vaccin Immunother.2014; 10(6): 1712–20. https://doi.org/10.4161/hv.28621 PMID: 24784118

89. Laryea DO, Abbeyquaye Parbie E, Frimpong E. Timeliness of childhood vaccine uptake among children attending a tertiary health service facility-based immunisation clinic in Ghana. BMC public health 2014; 14: 90. https://doi.org/10.1186/1471-2458-14-90 PMID: 24476339

90. Schoeps A, Ouedraogo N, Kagone M, Sie A, Muller O, Becher H. Socio-demographic determinants of timely adherence to BCG, Penta3, measles, and complete vaccination schedule in Burkina Faso. Vaccine 2013; 32(1): 96–102. https://doi.org/10.1016/j.vaccine.2013.10.063 PMID: 24183978

91. Ouédraogo N., Kagoné M., Sié A., Becher H., Müller O. Timeliness and Out-of-Sequence Vaccination among Young Children in Burkina Faso–Analysis of Health and Demographic Surveillance System (HDSS) Data. International Journal of TROPICAL DISEASE & Health 2013; 3(1): 45–56.

92. Ettarh RR, Mutua MK, Kyobutungi C. Ethnicity and delay in measles vaccination in a nairobi slum. Trop Med Health. 2012; 40(2): 59–62. https://doi.org/10.2149/tmh.2012-09s PMID: 23097621

93. Sadoh AE, Eregie CO. Timeliness and completion rate of immunization among Nigerian children attending a clinic-based immunization service. J Health Popul Nutr. 2009; 27(3): 391–5. https://doi.org/10.3329/jhpn.v27i3.3381 PMID: 19507754

94. Borus PK. Missed opportunities and inappropriately given vaccines reduce immunisation coverage in facilities that serve slum areas of Nairobi. East Afr Med J 2004; 81(3): 124–9. https://doi.org/10.4314/eamj.v81i3.9140 PMID: 15293969

95. Hasanain FH, Jan MM. Delays in primary vaccination of infants living in Western Saudi Arabia. Saudi Medical Journal 2002; 23(9): 1087–9. PMID: 12370718

96. Sartori AL, Minamisava R, Afonso ET, Policena GM, Pessoni GC, Bierrenbach AL, et al. Timeliness and risk factors associated with delay for pneumococcal conjugate 10-valent routine immunization in Brazilian children. Vaccine 2017; 35(7): 1030–6. https://doi.org/10.1016/j.vaccine.2017.01.012 PMID: 28108230

97. Bani Salameh AK, Malak MZ, Abu Adas MH. Factors associating vaccination delay among Jordanian children under two years of age. J Pediatr Nurs. 2021. https://doi.org/10.1016/j.pedn.2021.01.005 PMID: 33500152

98. Wagner AL, Shenton LM, Gillespie BW, Mathew JL, Boulton ML. Assessing the timeliness of vaccine administration in children under five years in India, 2013. Vaccine 2019; 37(4): 558–64. https://doi.org/10.1016/j.vaccine.2018.12.035 PMID: 30595345

99. Nadella P, Smith ER, Muhihi A, Noor RA, Masanja H, Fawzi WW, et al. Determinants of delayed or incomplete diphtheria-tetanus-pertussis vaccination in parallel urban and rural birth cohorts of 30,956 infants in Tanzania. BMC Infect Dis. 2019; 19(1): 188. https://doi.org/10.1186/s12879-019-3828-3 PMID: 30808282

100. Banjari MA, Alamri AA, Algarni AY, Abualjadayel MH, Alshardi YS, Alahmadi TS. How often do children receive their vaccinations late, and why? Saudi Med J. 2018; 39(4): 347–53. https://doi.org/10.15537/smj.2018.4.21473 PMID: 29619485

101. Kaji A, Parker D, Chu C, Thayatkawin W, Suelaor J, Charatrueangrongkun R, et al. Immunization Coverage in Migrant School Children Along the Thailand-Myanmar Border. J Immigr Minor Health. 2016; 18(5): 1038–45. https://doi.org/10.1007/s10903-015-0294-x PMID: 26483180

102. Sood RK., Sood A., Bharti OK, Ramachandran V, Phull A. High Immunization Coverage but Delayed Immunization Reflects Gaps in Health Management Information System (HMIS) in District Kangra, Himachal Pradesh, India—An Immunization Evaluation. World Journal of Vaccines 2015; 5: 69–78.

103. Saraiva FO, Minamisava R, Vieira MAdS, Bierrenbach AL, Andrade AL. Vaccination Coverage and Compliance with Three Recommended Schedules of 10-Valent Pneumococcal Conjugate Vaccine during the First Year of Its Introduction in Brazil: A Cross-Sectional Study. PloS one 2015; 10(6): e0128656. https://doi.org/10.1371/journal.pone.0128656 PMID: 26061276

104. Gentile A, Juarez M, Hernandez S, Moya A, Bakir J, Lucion M. Influenza vaccine: Delayed vaccination schedules and missed opportunities in children under 2 years old. Vaccine 2015; 33(32): 3913–7. https://doi.org/10.1016/j.vaccine.2015.06.065 PMID: 26116256

105. Li Q, Hu Y, Zhong Y, Chen Y, Tang X, Guo J, et al. Using the Immunization Information System to determine vaccination coverage rates among children aged 1–7 years: a report from Zhejiang Province, China. Int J Environ Res Public Health. 2014; 11(3): 2713–28. https://doi.org/10.3390/ijerph110302713 PMID: 24603495

106. Odusanya OO. Age-appropriate immunization coverage in a rural community in Edo State, Nigeria. Journal of the Nigerian Infection Control Association 2000; 3(2): 9.

107. Hu Y, Chen Y, Wang Y, Liang H, Lv H. Age-appropriate vaccination coverage and its determinants for the polio containing vaccine 1–3 and measles-containing vaccine doses in Zhejiang province, China: A community-based cross-sectional study. Hum Vaccin Immunother.2020; 16(9): 2257–64. https://doi.org/10.1080/21645515.2020.1718439 PMID: 32048897

108. Hu Y, Wang Y, Chen Y, Liang H, Chen Z. Measles vaccination coverage, determinants of delayed vaccination and reasons for non-vaccination among children aged 24–35 months in Zhejiang province, China. BMC public health 2018; 18(1): 1298. https://doi.org/10.1186/s12889-018-6226-7 PMID: 30482185

109. Shrivastwa N, Gillespie BW, Lepkowski JM, Boulton ML. Vaccination Timeliness in Children Under India's Universal Immunization Program. Pediatr Infect Dis J. 2016; 35(9): 955–60. https://doi.org/10.1097/INF.0000000000001223 PMID: 27195601

110. Mohammed A, Aqeel A. Impact of the COVID-19 pandemic on routine childhood immunization in Saudi Arabia. Vaccines 2020; 8(4).

111. Mthiyane TN, Cohen C, Norris SA, Walaza S, Tempia S, Cohen AL, et al. Factors associated with missed and delayed DTP3 vaccination in children aged 12–59 months in two communities in South

Africa, 2012–2013. S Afr Med J. 2019; 109(8): 562–9. https://doi.org/10.7196/SAMJ.2019.v109i8.13244 PMID: 31456549

112. Marefiaw TA, Yenesew MA, Mihirete KM. Age-appropriate vaccination coverage and its associated factors for pentavalent 1–3 and measles vaccine doses, in northeast Ethiopia: A community-based cross-sectional study. PloS one 2019; 14(8): e0218470. https://doi.org/10.1371/journal.pone.0218470 PMID: 31419230

113. Tauil MD, Sato APS, Costa AA, Inenami M, Ferreira VLD, Waldman EA. Vaccination coverage according to doses received and timely administered based on an electronic immunization registry, Araraquara-SP, Brazil, 2012–2014. Epidemiol Serv Saude.2017; 26(4): 835–46. https://doi.org/10.5123/S1679-49742017000400014 PMID: 29211146

114. Hu Y, Chen E, Li Q, Chen Y, Qi X. Immunization coverage and its determinants among children born in 2008–2009 by questionnaire survey in Zhejiang, China. Asia Pac J Public Health. 2015; 27(2): NP1132–43. https://doi.org/10.1177/1010539511430995 PMID: 22186397

115. Lin W, Xiong Y, Tang H, Chen B, Ni J. Factors associated with delayed measles vaccination among children in Shenzhen, China: a case-control study. Hum Vaccin Immunother. 2014; 10(12): 3601–6. https://doi.org/10.4161/21645515.2014.979687 PMID: 25668667

116. Hu Y, Chen Y, Guo J, Tang X, Shen L. Completeness and timeliness of vaccination and determinants for low and late uptake among young children in eastern China. Hum Vaccin Immunother. 2014; 10(5): 1408–15. https://doi.org/10.4161/hv.28054 PMID: 24584000

117. Han K, Zheng H, Huang Z, Qiu Q, Zeng H, Chen B, et al. Vaccination coverage and its determinants among migrant children in Guangdong, China. BMC public health 2014; 14: 203. https://doi.org/10.1186/1471-2458-14-203 PMID: 24568184

118. Calhoun LM, Eijk AMv, Lindblade KA, Odhiambo FO, Wilson ML, Winterbauer E, et al. Determinants and coverage of vaccination in children in Western Kenya from a 2003 cross-sectional survey. Am J Trop Med Hyg 2014; 90(2): 234–41. https://doi.org/10.4269/ajtmh.13-0127 PMID: 24343886

119. Le Polain de Waroux O, Schellenberg JRA, Manzi F, Mrisho M, Shirima K, Mshinda H, et al. Timeliness and completeness of vaccination and risk factors for low and late vaccine uptake in young children living in rural southern Tanzania. Int Health. 2013; 5(2): 139–47. https://doi.org/10.1093/inthealth/iht006 PMID: 24030114

120. Hu Y, Li Q, Luo S, Lou L, Qi X, Xie S. Timeliness vaccination of measles containing vaccine and barriers to vaccination among migrant children in East China. PloS one 2013; 8(8): e73264. https://doi.org/10.1371/journal.pone.0073264 PMID: 24013709

121. Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. J Epidemiol Community Health. 2012; 66(7): e14. https://doi.org/10.1136/jech.2010.124651 PMID: 21551179

122. Cui F, Gofin R. Immunization coverage and its determinants in children aged 12–23 months in Gansu, China. Vaccine 2007; 25(4): 664–71. https://doi.org/10.1016/j.vaccine.2006.08.027 PMID: 17049682

123. Chen CJ, Bakeera-Kitaka S, Mupere E, Kasirye P, Munube D, Idro R, et al. Paediatric immunisation and chemoprophylaxis in a Ugandan sickle cell disease clinic. J Paediatr Child Health. 2019; 55(7): 795–801. https://doi.org/10.1111/jpc.14291 PMID: 30411430

124. Dionne-Odom J, Westfall AO, Nzuobontane D, et al. Predictors of Infant Hepatitis B Immunization in Cameroon: Data to Inform Implementation of a Hepatitis B Birth Dose. Pediatr Infect Dis J. 2018; 37(1): 103–7. https://doi.org/10.1097/INF.0000000000001728 PMID: 28787383

125. Lausevic D, Tiodorovic B, Rakocevic B, Medenica S, Beatovic V, Hadzifejzovic A. Timeliness and level of primary immunisation coverage against diphtheria, whooping cough and tetanus in Montenegro. Acta Facultatis Medicae Naissensis 2009; 26(3): 113–9.

126. Yang X, Tang T, Yang Z, Liu L, Yuan S, Zhang T. Evaluation of measles vaccination coverage in Lincang City, Yunnan Province, China. Hum Vaccin Immunother 2021; 17(9): 3145–52. https://doi.org/10.1080/21645515.2021.1911215 PMID: 33847247

127. Woldu Anbesu E, Abubeker SA, Berhe BM. Age-appropriate vaccination practice and associated factors among mothers of children aged less than one year in the pastoral community of Afar region, Ethiopia. Hum Vaccin Immunother 2021; 17(9): 3178–85. https://doi.org/10.1080/21645515.2021.1919480 PMID: 34062099

128. Tang XY, Yan XX, Wei X, Qin QL, Lin YD, Geater A, et al. Timeliness, completeness, and timeliness-and-completeness of serial routine vaccinations among rural children in Southwest China: A multi-stage stratified cluster sampling survey. Vaccine 2021; 39(24): 3236–49. https://doi.org/10.1016/j.vaccine.2021.04.048 PMID: 33966907

129. Musa S, Bach Habersaat K, Jackson C, Kulo A, Primorac E, Smjecanin M, et al. Tailoring Immunization Programmes: using patient file data to explore vaccination uptake and associated factors. Hum Vaccin Immunother. 2021; 17(1): 228–36. https://doi.org/10.1080/21645515.2020.1769396 PMID: 32574138

130. Li M, Ji C, Zeng Y, Yao D, Wang X, Shao J. Reasons of the delayed vaccination, recommendations and safety of vaccination in children with congenital heart disease in Zhejiang, China. Human vaccines & immunotherapeutics 2021: 1–7. https://doi.org/10.1080/21645515.2021.1872343 PMID: 33577372

131. Kagucia EW, Ochieng B, Were J, Hayford K, Obor D, O'Brien KL, et al. Impact of mobile phone delivered reminders and unconditional incentives on measles-containing vaccine timeliness and coverage: a randomised controlled trial in western Kenya. BMJ Glob Health. 2021; 6(1). https://doi.org/10.1136/bmjgh-2020-003357 PMID: 33509838

132. Jain R, Chopra A, Falézan C, Patel M, Dupas P. COVID-19 related immunization disruptions in Rajasthan, India: A retrospective observational study. Vaccine 2021; 39(31): 4343–50. https://doi.org/10.1016/j.vaccine.2021.06.022 PMID: 34154863

133. Huynh G, Pham LA, Tran TT, Cao NN, Nguyen TNH, Bui QV. How knowledge of hepatitis B disease and vaccine influences vaccination practices among parents in Ho Chi Minh City, Vietnam. Asian Pacific Journal of Tropical Medicine 2021; 14(3): 122–7.

134. Mutua MK, Mohamed SF, Kimani-Murage EW, Kiarie L, Janusz CB, Aaby P, et al. Complete and on-time routine childhood immunisation: determinants and association with severe morbidity in urban informal settlements, Nairobi, Kenya. Ann Hum Biol. 2020; 47(2): 132–41. https://doi.org/10.1080/03014460.2020.1725121 PMID: 32429760

135. Loy S, Cheung Y, Chan K, Soh SE, Godfrey KM, Tan KH, et al. Timeliness of childhood vaccination coverage: the growing up in Singapore towards healthy outcomes study. Prev Sci. 2020; 21(3): 283–92. https://doi.org/10.1007/s11121-019-01078-2 PMID: 31960261

136. Li J, Yu W, Zhao Z, Zhang L, Gong Q. Measles vaccination among children in border areas of Yunnan Province, Southwest China. PloS one 2020; 15(10): e0240733. https://doi.org/10.1371/journal.pone.0240733 PMID: 33085692

137. Li AJ, Tabu C, Shendale S, Sergon K, Okoth PO, Mugoya IK, et al. Assessment of missed opportunities for vaccination in Kenyan health facilities, 2016. PloS one 2020; 15(8): e0237913. https://doi.org/10.1371/journal.pone.0237913 PMID: 32817630

138. Alkoshi S, Leshem E. Lower Coverage Rates of Full Rotavirus Vaccine Series in Libyan Children: A Prospective Cross-Sectional Study, 2016. Iranian Journal of Public Health 2020; 49(3): 487–94.

139. Qazi U, Malik S, Raza UA, Saad M, Zeeshan MF, Anwar S. Compliance to timely vaccination in an Expanded Program on Immunization center of Pakistan. Vaccine 2019; 37(32): 4618–22. https://doi.org/10.1016/j.vaccine.2018.01.044 PMID: 29395529

140. Noh J-W, Kim Y-M, Akram N, Yoo KB, Cheon J, Lee LJ, et al. Determinants of timeliness in early childhood vaccination among mothers with vaccination cards in Sindh province, Pakistan: a secondary analysis of cross-sectional survey data. BMJ open 2019; 9(9): e028922. https://doi.org/10.1136/bmjopen-2019-028922 PMID: 31537561

141. Nakatudde I, Rujumba J, Namiiro F, Sam A, Mugalu J, Musoke P. Vaccination timeliness and associated factors among preterm infants at a tertiary hospital in Uganda. PloS one 2019; 14(9): e0221902. https://doi.org/10.1371/journal.pone.0221902 PMID: 31490987

142. Mensah K, Heraud JM, Takahashi S, Winter AK, Metcalf CJE, Wesolowski A. Seasonal gaps in measles vaccination coverage in Madagascar. Vaccine 2019; 37(18): 2511–9. https://doi.org/10.1016/j.vaccine.2019.02.069 PMID: 30940486

143. Lindqvist H, Duminda Guruge GN, Trollfors B. Age appropriateness of vaccination with recommended childhood vaccines in Sri Lanka. Vaccine: X 2019; 2: 100016. https://doi.org/10.1016/j.jvacx.2019.100016 PMID: 31384739

144. Kidanne L, Solomon M, Bisrat F, Asres M, Tadesse T, Asress A, et al. Child vaccination timing, intervals and missed opportunities in pastoral and semi-pastoral areas in Ethiopia. Ethiopian Journal of Health Development 2019; 33(3): 9.

145. Ibraheem R, Abdulkadir M, Akintola M, Adeboye M. Determinants of Timely Presentation for Birth Dose Vaccination at an Immunization Centre in North-central Nigeria. Ann Glob Health. 2019; 85(1). https://doi.org/10.5334/aogh.725 PMID: 30873798

146. Giao H, Quang Vinh B, Huynh Tam Lang N, Le An P. Parents' Attitude about Hepatitis B Disease and Practice of Hepatitis B Vaccination among Children in Ho Chi Minh City, Vietnam. Biomed Res Int. 2019; 2019: 9323814. https://doi.org/10.1155/2019/9323814 PMID: 31355286

147. Boulton ML, Carlson BF, Wagner AL, Porth JM, Gebremeskel B, Abeje Y. Vaccination timeliness among newborns and infants in Ethiopia. PloS one 2019; 14(2): e0212408. https://doi.org/10.1371/journal.pone.0212408 PMID: 30779781

148. Sheikh N, Sultana M, Ali N, Akram R, Mahumud RA, Asaduzzaman M, et al. Coverage, Timelines, and Determinants of Incomplete Immunization in Bangladesh. Trop Med Infect Dis. 2018; 3(3).

149. Pertet AM, Kaseje D, Otieno-Odawa CF, Kirika L, Wanjala C, Ochieng J, et al. Under vaccination of children among Maasai nomadic pastoralists in Kenya: is the issue geographic mobility, social demographics or missed opportunities? BMC public health 2018; 18(1): 1389. https://doi.org/10.1186/s12889-018-6309-5 PMID: 30567528

150. Masters NB, Tefera YA, Wagner AL, Boulton ML. Vaccine hesitancy among caregivers and association with childhood vaccination timeliness in Addis Ababa, Ethiopia. Hum Vaccin Immunother. 2018; 14(10): 2340–7. https://doi.org/10.1080/21645515.2018.1480242 PMID: 29792555

151. Choudhary M, Solomon R, Awale J, Dey R. Demand-side determinants of timely vaccination of oral polio vaccine in social mobilization network areas of CORE Group polio project in Uttar Pradesh, India. BMC Infect Dis.s 2018; 18(1): 222.

152. Bondo A, Nambiar B, Lufesi N, Deula R, King C, Masache G, et al. An assessment of PCV13 vaccine coverage using a repeated cross-sectional household survey in Malawi. Gates Open Res. 2018; 2: 37. https://doi.org/10.12688/gatesopenres.12837.1 PMID: 30569035

153. Belmar-George S, Cassius-Frederick J, Leon P, Alexander S, Holder Y, Lewis-Bell KN, et al. MMR2 vaccination coverage and timeliness among children born in 2004–2009: a national survey in Saint Lucia, 2015. Rev Panam Salud Publica. 2018; 42: e76. https://doi.org/10.26633/RPSP.2018.76 PMID: 31093104

154. Zivich PN, Kiketa L, ry, Kawende B, Lapika B, Yotebieng M. Vaccination Coverage and Timelines Among Children 0–6 Months in Kinshasa, the Democratic Republic of Congo: A Prospective Cohort Study. Matern Child Health J. 2017; 21(5): 1055–64. https://doi.org/10.1007/s10995-016-2201-z PMID: 28058663

155. Tippins A, Leidner AJ, Meghani M, Griffin A, Helgenberger L, Nyaku M, et al. Timeliness of childhood vaccination in the Federated States of Micronesia. Vaccine 2017; 35(47): 6404–11. https://doi.org/10.1016/j.vaccine.2017.10.001 PMID: 29029941

156. Tang XY, Geater A, McNeil E, Zhou HX, Deng QY, Dong AH. Timeliness and completeness of measles vaccination among children in rural areas of Guangxi, China: A stratified three-stage cluster survey. J Epidemiol.2017; 27(7): 317–24. https://doi.org/10.1016/j.je.2016.08.006 PMID: 28187960

157. Ni ZL, Tan XD, Shao HY, Wang Y. Immunisation status and determinants of left-behind children aged 12–72 months in central China. Epidemiol Infect. 2017; 145(9): 1763–72. https://doi.org/10.1017/S0950268817000589 PMID: 28357974

158. Narvaez J, Osorio MB, Castaneda-Orjuela C, Alvis Zakzuk N, Cediel N, Chocontá-Piraquive LÁ, et al. Is Colombia reaching the goals on infant immunization coverage? A quantitative survey from 80 municipalities. Vaccine 2017; 35(11): 1501–8. https://doi.org/10.1016/j.vaccine.2017.01.073 PMID: 28209436

159. Kumar D, Sharma S, Bhardwaj AK. Age-Appropriate Immunization (AAI) as an Intractable Issue Subsequent to Coverage. Ann Med Health Sci Res 2017; 7(2): 73–6.

160. Hu Y, Chen Y, Zhang B. Two-dose seasonal influenza vaccine coverage and timeliness among children aged 6 months through 3 years: An evidence from the 2010–11 to the 2014–15 seasons in Zhejiang province, east China. Hum Vaccin Immunother. 2017; 13(1): 75–80. https://doi.org/10.1080/21645515.2016.1225640 PMID: 27624854

161. Wagner AL, Sun X, Huang Z, Ren J, Mukherjee B, Wells EV, et al. On-time measles and pneumococcal vaccination of Shanghai children: the impact of individual-level and neighborhood-level factors. Pediatr Infect Dis J. 2016; 35(10): e311–e7. https://doi.org/10.1097/INF.0000000000001267 PMID: 27294307

162. Tsega A, Hausi H, Chriwa G, Steinglass R, Smith D, Valle M. Vaccination coverage and timely vaccination with valid doses in Malawi. Vaccine Reports 2016; 6: 8–12.

163. Tang X, Geater A, McNeil E, Zhou H, Deng Q, Dong A, et al. Parental migration and children's timely measles vaccination in rural China: a cross-sectional study. Trop Med Int Health. 2016; 21(7): 886–94. https://doi.org/10.1111/tmi.12719 PMID: 27137758

164. Schweitzer A, Pessler F, Akmatov MK. Impact of rotavirus vaccination on coverage and timing of pentavalent vaccination—Experience from 2 Latin American countries. Hum Vaccin Immunother. 2016; 12(5): 1250–6. https://doi.org/10.1080/21645515.2015.1127486 PMID: 26833132

165. Mvula H, Heinsbroek E, Chihana M, Crampin AC, Kabuluzi S, Chirwa G, et al. Predictors of uptake and timeliness of newly introduced pneumococcal and rotavirus vaccines, and of measles vaccine in rural Malawi: a population cohort study. PLoS ONE 2016; 11(5): e0154997. https://doi.org/10.1371/journal.pone.0154997 PMID: 27152612

166. Dao Thi Minh A, Hoang Van M, Nguyen Thi Huyen T, Thu Huong NT, Nam YS, Van Dung D et al. Timely immunization completion among children in Vietnam from 2000 to 2011: a multilevel analysis of individual and contextual factors. Glob Health Action. 2016; 9: 1–11.

167. Chung H, Han S, Kim H, Finkelstein JL. Childhood immunizations in China: disparities in health care access in children born to North Korean refugees. BMC Int Health Hum Rights. 2016; 16(13). https://doi.org/10.1186/s12914-016-0085-z PMID: 27074957

168. Rammohan A, Awofeso N. District-level variations in childhood immunizations in India: The role of socio-economic factors and health infrastructure. Soc Sci Med. (1982) 2015; 145: 163–72. https://doi.org/10.1016/j.socscimed.2015.05.004 PMID: 25958173

169. Odutola A, Afolabi MO, Ogundare EO, Lowe-Jallow YN, Worwui A, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. BMC Health Serv Res. 2015; 15: 346. https://doi.org/10.1186/s12913-015-1015-9 PMID: 26315547

170. Ochoa TJ, Zea-Vera A, Bautista R, et al. Vaccine schedule compliance among very low birth weight infants in Lima, Peru. Vaccine 2015; 33(2): 354–8. https://doi.org/10.1016/j.vaccine.2014.11.014 PMID: 25448091

171. Montgomery JP, Zhang Y, Carlson B, Ewing S, Wang X, Boulton ML. Measles vaccine coverage and series completion among children 0–8 years of age in Tianjin, China. Pediatr Infect Dis J 2015; 34(3): 289–95. https://doi.org/10.1097/INF.0000000000000562 PMID: 25259932

172. Mokhtari M, Rezaeimanesh M, Mohammadbeigi A, Zahraei SM, Mohammadsalehi N, Ansari H. Risk Factors of Delay Proportional Probability in Diphtheria-tetanus-pertussis Vaccination of Iranian Children; Life Table Approach Analysis. J Glob Infect Dis. s 2015; 7(4): 165–9. https://doi.org/10.4103/0974-777X.170503 PMID: 26752871

173. Mohammadbeigi A, Mokhtari M, Zahraei SM, Eshrati B, Rejali M. Survival Analysis for Predictive Factors of Delay Vaccination in Iranian Children. Int J Prev Med. 2015; 6: 119. https://doi.org/10.4103/2008-7802.170868 PMID: 26900433

174. Gill KP, Priyanka D. Impact of socio-demographic factors on age appropriate immunization of infants in slums of Amritsar city (Punjab), India. National Journal of Community Medicine 2015; 6(1): 11–5.

175. Delrieu I, Gessner BD, Baril L, Bahmanyar ER. From current vaccine recommendations to everyday practices: an analysis in five sub-Saharan African countries. Vaccine 2015; 33(51): 7290–8. https://doi.org/10.1016/j.vaccine.2015.10.107 PMID: 26546260

176. Barman MP, Krishnajyoti N, Jiten H. Factors affecting timeliness of immunization coverage among children of Assam, India: a cross-sectional study. Journal of Health Management 2015; 17(3): 274–84.

177. Bangure D, Chirundu D, Gombe N, Marufu T, Mandozana G, Tshimanga M, et al. Effectiveness of short message services reminder on childhood immunization programme in Kadoma, Zimbabwe—a randomized controlled trial, 2013. BMC Public Health. 2015; 15: 137. https://doi.org/10.1186/s12889-015-1470-6 PMID: 25885862

178. Akmatov MK, Kimani-Murage E, Pessler F, Guzman CA, Krause G, Kreienbrock L, et al. Evaluation of invalid vaccine doses in 31 countries of the WHO African Region. Vaccine 2015; 33(7): 892–901. https://doi.org/10.1016/j.vaccine.2014.10.089 PMID: 25523526

179. Wagner AL, Zhang Y, Montgomery JP, Ding Y, Carlson BF, Boulton ML. Timely measles vaccination in Tianjin, China: a cross-sectional study of immunization records and mothers. BMC public health 2014; 14: 888. https://doi.org/10.1186/1471-2458-14-888 PMID: 25168663

180. Suarez-Castaneda E, Pezzoli L, Elas M, Baltrons R, Crespin-Elías EO, Pleitez OA, et al. Routine childhood vaccination programme coverage, El Salvador, 2011—in search of timeliness. Vaccine 2014; 32(4): 437–44. https://doi.org/10.1016/j.vaccine.2013.11.072 PMID: 24315884

181. Scott S, Odutola A, Mackenzie G, et al. Coverage and timing of children's vaccination: an evaluation of the expanded programme on immunisation in The Gambia. PLoS One 2014; 9(9): e107280. https://doi.org/10.1371/journal.pone.0107280 PMID: 25232830

182. Rammohan A, Awofeso N, Iqbal K. Gender-differentials in the timing of measles vaccination in rural India. Demographic Research 2014; 30: 1825–48.

183. Kang WY, Ding ZR, Shen LP, Zhao Z, Huang G, Zhang J, et al. Risk factors associated with immunoprophylaxis failure against mother to child transmission of hepatitis B virus and hepatitis B vaccination status in Yunnan province, China. Vaccine 2014; 32(27): 3362–6. https://doi.org/10.1016/j.vaccine.2014.04.045 PMID: 24793939

184. Park Y, Eom H, Kim E, Choe Y, Bae G, Lee D. Reemergence of measles in South Korea: implications for immunization and surveillance programs. Jpn J Infect Dis. 2013; 66(1): 6–10. https://doi.org/10.7883/yoken.66.6 PMID: 23429077

185. Flannery B, Samad S, Moraes JCd, Tate JE, Danovaro-Holliday MC, de Oliveira LH, et al. Uptake of oral rotavirus vaccine and timeliness of routine immunization in Brazil's National Immunization Program. Vaccine 2013; 31(11): 1523–8. https://doi.org/10.1016/j.vaccine.2013.01.004 PMID: 23313652

186. Awofeso N, Rammohan A, Iqbal K. Age-appropriate vaccination against measles and DPT-3 in India—closing the gaps. BMC public health 2013; 13: 358. https://doi.org/10.1186/1471-2458-13-358 PMID: 23594400

187. Uner S, Ozelci P, Com S, Kosdak M, Mollahaliloglu S, Erkoc Y. Vaccine coverage rates among 12–23 month old children living in four selected provinces of turkey: Results of a lot quality survey. Turkiye Klinikleri Journal of Medical Sciences 2012; 32(4): 952–62.

188. Babirye JN, Engebretsen IMS, Makumbi F, Fadnes LT, Wamani H, Tylleskar T, et al. Timeliness of childhood vaccinations in Kampala Uganda: a community-based cross-sectional study. PloS one 2012; 7(4): e35432. https://doi.org/10.1371/journal.pone.0035432 PMID: 22539972

189. Park B, Lee YK, Cho LY, Go UY, Yang JJ, Ma SH, et al. Estimation of Nationwide Vaccination Coverage and Comparison of Interview and Telephone Survey Methodology for Estimating Vaccination Status. J Korean Med Sci 2011; 26(6): 711–9. https://doi.org/10.3346/jkms.2011.26.6.711 PMID: 21655054

190. Fadnes LT, Nankabirwa V, Sommerfelt H, Tylleskar T, Tumwine JK, Engebretsen IMS. Is vaccination coverage a good indicator of age-appropriate vaccination? A prospective study from Uganda. Vaccine 2011; 29(19): 3564–70. https://doi.org/10.1016/j.vaccine.2011.02.093 PMID: 21402043

191. Fadnes LT, Jackson D, Engebretsen IM, Zembe W, Sanders D, Sommerfelt H, et al. Vaccination coverage and timeliness in three South African areas: a prospective study. BMC public health 2011; 11: 404. https://doi.org/10.1186/1471-2458-11-404 PMID: 21619642

192. Toikilik S, Tuges G, Lagani J, Wafiware E, Posanai E, Coghlan B, et al. Are hard-to-reach populations being reached with immunization services? Findings from the 2005 Papua New Guinea national immunization coverage survey. Vaccine 2010; 28(29): 4673–9. https://doi.org/10.1016/j.vaccine.2010.04.063 PMID: 20451641

193. Sun M, Ma R, Zeng Y, Luo F, Zhang J, Hou W. Immunization status and risk factors of migrant children in densely populated areas of Beijing, China. Vaccine 2010; 28(5): 1264–74. https://doi.org/10.1016/j.vaccine.2009.11.015 PMID: 19941996

194. Siddiqi N, Siddiqi A-e-a, Nisar N, Khan A. Mothers' knowledge about EPI and its relation with age-appropriate vaccination of infants in peri-urban Karachi. J Pak Med Assoc. 2010; 60(11): 940–4. PMID: 21375199

195. Prinja S, Gupta M, Singh A, Kumar R. Effectiveness of planning and management interventions for improving age-appropriate immunization in rural India. Bull World Health Organ. 2010; 88(2): 97–103. https://doi.org/10.2471/BLT.08.059543 PMID: 20428366

196. Corsi DJ, Bassani DG, Kumar R, Awasthi S, Jotkar R, Kaur N, et al. Gender inequity and age-appropriate immunization coverage in India from 1992 to 2006. BMC Int Health Hum Rights. 2009; 9: S3. https://doi.org/10.1186/1472-698X-9-S1-S3 PMID: 19828061

197. Siddiqi N, Altaf K, Nighat N, Siddiqi A. Assessment of EPI (Expanded program of immunization) vaccine coverage in a peri-urban area. J Pak Med Assoc. 2007; 57(8): 391–5. PMID: 17902521

198. Senessie C, Gage GN, Elm Ev. Delays in childhood immunization in a conflict area: a study from Sierra Leone during civil war. Confl Health. 2007; 1(14).

199. Datar A, Mukherji A, Sood N. Health infrastructure & immunization coverage in rural India. The Indian J Med Res. 2007; 125(1): 31–42. PMID: 17332655

200. Dayan GH, Shaw KM, Baughman AL, Orellana LC, Forlenza R, Ellis A, et al. Assessment of delay in age-appropriate vaccination using survival analysis. Am J Epidemiol. 2006; 163(6): 561–70. https://doi.org/10.1093/aje/kwj074 PMID: 16421238

201. Al-Shemari. Causes of Delay in Age Appropriate Vaccination. The Iraqi Postgraduate Medical Journal 2006; 5(3): 298–301.

202. Kahn JG, Mokdad AH, Deming MS, Roungou JB, Boby AM, Excler JL, et al. Avoiding missed opportunities for immunization in the Central African Republic: potential impact on vaccination coverage. Bull World Health Organ 1995; 73(1): 47–55. PMID: 7704925

203. Yang Y, Wang Y, Yang D, Dong S, Yang Y, Zhu X, et al. Factors associated with uptake of Haemophilus influenzae type b vaccination in Shanghai, China. BMC Pediatr. 2019; 19(1): 8. https://doi.org/10.1186/s12887-018-1374-6 PMID: 30616637

204. Wagner AL, Sun X, Montgomery JP, Huang Z, Boulton ML. The impact of residency and urbanicity on Haemophilus influenzae Type b and pneumococcal immunization in Shanghai Children: a Retrospective Cohort Study. PloS one 2014; 9(5): e97800. https://doi.org/10.1371/journal.pone.0097800 PMID: 24828814

205. Patel MK, Calvez El, Wannemuehler K, Segalin JM. Hepatitis B vaccination coverage and prevalence of hepatitis B surface antigen among children in French Polynesia, 2014. Am J Trop Med Hyg. 2016; 94(6): 1370–5. https://doi.org/10.4269/ajtmh.15-0903 PMID: 27001757

206. Sato R. Association between access to a health facility and continuum of vaccination behaviors among Nigerian children. Hum Vaccin Immunother. 2020; 16(5): 1215–20. https://doi.org/10.1080/21645515.2019.1678360 PMID: 31634047

207. Oladepo O, Dipeolu IO, Oladunni O. Outcome of reminder text messages intervention on completion of routine immunization in rural areas, Nigeria. Health Promot Int. 2020.

208. Danya Arif S, Rozina Feroz A, Mubarak Taighoon S, Aamir Javed K, Subhash C, ir. Effect of vaccine reminder and tracker bracelets on routine childhood immunization coverage and timeliness in urban Pakistan (2017–18): a randomized controlled trial. BMC Public Health 2020; 20(1086). https://doi.org/10.1186/s12889-020-09088-4 PMID: 32652969

209. Domek GJ, Contreras-Roldan IL, Bull S, O'Leary ST, Bolaños Ventura GA, Bronsert M, et al. Text message reminders to improve infant immunization in Guatemala: A randomized clinical trial. Vaccine 2019; 37(42): 6192–200. https://doi.org/10.1016/j.vaccine.2019.08.046 PMID: 31492475

210. Vasudevan L, Labrique AB, Mehra S, Wu L, Levine O, Feikin D, et al. Maternal determinants of timely vaccination coverage among infants in rural Bangladesh. Vaccine 2014; 32(42): 5514–9. https://doi.org/10.1016/j.vaccine.2014.06.092 PMID: 25132336

211. Igarashi K, Sasaki S, Fujino Y, Tanabe N, Muleya CM, Tambatamba B, et al. The impact of an immunization programme administered through the Growth Monitoring Programme Plus as an alternative way of implementing Integrated Management of Childhood Illnesses in urban-slum areas of Lusaka, Zambia. Trans R Soc Trop Med Hyg. 2010; 104(9): 577–82. https://doi.org/10.1016/j.trstmh.2010.05.008 PMID: 20609454

212. Levine G, Salifu A, Mohammed I, Fink G. Mobile nudges and financial incentives to improve coverage of timely neonatal vaccination in rural areas (GEVaP trial): A 3-armed cluster randomized controlled trial in Northern Ghana. PLoS One 2021; 16(5): e0247485. https://doi.org/10.1371/journal.pone.0247485 PMID: 34010312

213. Kyuregyan KK, Kichatova VS, Isaeva OV, Potemkin IA, Malinnikova EY, Lopatukhina MA, et al. Coverage with Timely Administered Vaccination against Hepatitis B Virus and Its Influence on the Prevalence of HBV Infection in the Regions of Different Endemicity. Vaccines 2021; 9(2). https://doi.org/10.3390/vaccines9020082 PMID: 33498794

214. Singh C, Mishra A, Agarwal N, Lohani P, Ayub A, Mishra S. Timeliness of childhood vaccination and its decisive factors in Bihar: A community-based study. Journal of Clinical and Diagnostic Research 2020; 14(2): LC05–LC9.

215. He Y, Liu Y, Dai B, Zhao L, Lin J, Yang J, et al. Assessing vaccination coverage, timeliness, and its temporal variations among children in a rural area in China. Hum Vaccin Immunother. 2020: 1–9.

216. Wallace AS, Peetosutan K, Untung A, Ricardo M, Yosephine P, Wannemuehler K, et al. Home-based records and vaccination appointment stickers as parental reminders to reduce vaccination dropout in Indonesia: A cluster-randomized controlled trial. Vaccine 2019; 37(45): 6814–23. https://doi.org/10.1016/j.vaccine.2019.09.040 PMID: 31564451

217. Ali EAAM, Aljawadi HFM. Adherence to the national immunization schedule for the first year of life in Misan, Iraq. Indian Journal of Public Health Research and Development 2019; 10(3): 459–64.

218. Pham TT, Le HM, Nguyen DT, Maertens K, Leuridan E, Theeten H, et al. Assessment of the timely administration of the hepatitis B and BCG birth dose and the primary infant vaccination schedule in 2015–2016 in the Mekong Delta, Viet Nam. Vaccine 2018; 36(38): 5760–5. https://doi.org/10.1016/j.vaccine.2018.08.002 PMID: 30121141

219. Noh JW, Kim YM, Akram N, Yoo KB, Park J, Cheon J, et al. Factors affecting complete and timely childhood immunization coverage in Sindh, Pakistan; A secondary analysis of cross- sectional survey data. Plos One 2018; 13(10): 15. https://doi.org/10.1371/journal.pone.0206766 PMID: 30379947

220. Mansour Z, Said R, Brandt L, Khachan J, Rady A, Fahmy K, et al., Factors affecting age-appropriate timeliness of vaccination coverage among children in Lebanon. Gates Open Res. 2018; 2: 71. https://doi.org/10.12688/gatesopenres.12898.1 PMID: 30734029

221. Hu Y, Li Q, Chen YP. Timeliness of Childhood Primary Immunization and Risk Factors Related with Delays: Evidence from the 2014 Zhejiang Provincial Vaccination Coverage Survey. Int J Environ Res Public Health. 2017; 14(9): 13. https://doi.org/10.3390/ijerph14091086 PMID: 28930165

222. Vonasek BJ, Bajunirwe F, Jacobson LE, Twesigye L, Dahm J, Grant MJ, et al. Do Maternal Knowledge and Attitudes towards Childhood Immunizations in Rural Uganda Correlate with Complete Childhood Vaccination? PloS one 2016; 11(2): e0150131. https://doi.org/10.1371/journal.pone.0150131 PMID: 26918890

223. O'Leary M, Thomas S, Hurt L, Floyd S, Shannon C, Newton S, et al. Vaccination timing of low-birth-weight infants in rural Ghana: a population-based, prospective cohort study. Bull World Health Organ. 2016; 94(6): 442–51D. https://doi.org/10.2471/BLT.15.159699 PMID: 27274596

224. Mutua MK, Kimani-Murage E, Ngomi N, Ravn H, Mwaniki P, Echoka E. Fully immunized child: coverage, timing and sequencing of routine immunization in an urban poor settlement in Nairobi, Kenya. Trop Med Health. h 2016; 44: 13.

225. Le Roux K, Akin-Olugbade O, Katzen LS, Laurenzi C, Mercer N, Tomlinson M, et al. Immunisation coverage in the rural Eastern Cape—are we getting the basics of primary care right? Results from a longitudinal prospective cohort study. S Afr Med J. 2016; 107(1): 52–5. https://doi.org/10.7196/SAMJ.2016.v107.i1.11242 PMID: 28112092

226. Hughes MM, Katz J, Englund JA, Khatry SK, Shrestha L, LeClerq SC, et al. Infant vaccination timing: beyond traditional coverage metrics for maximizing impact of vaccine programs, an example from southern Nepal. Vaccine 2016; 34(7): 933–41. https://doi.org/10.1016/j.vaccine.2015.12.061 PMID: 26788880

227. Rejali M, Mohammadbeigi A, Mokhtari M, Zahraei SM, Eshrati B. Timing and delay in children vaccination; evaluation of expanded program of immunization in outskirt of Iranian cities. J Res Health Sci. 2015; 15(1): 54–8. PMID: 25821027

228. Thysen SM, Byberg S, Pedersen M, Rodrigues A, Ravn H, Martins C, et al. BCG coverage and barriers to BCG vaccination in Guinea-Bissau: an observational study. BMC public health 2014; 14: 1037. https://doi.org/10.1186/1471-2458-14-1037 PMID: 25282475

229. Gram L, Soremekun S, Asbroek A, Manu A, O'Leary M, Hill Z, et al. Socio-economic determinants and inequities in coverage and timeliness of early childhood immunisation in rural Ghana. Trop Med Int Health. 2014; 19(7): 802–11. https://doi.org/10.1111/tmi.12324 PMID: 24766425

230. Fisker AB, Hornshoj L, Rodrigues A, Balde I, Fernandes M, Benn CS, et al. Effects of the introduction of new vaccines in Guinea-Bissau on vaccine coverage, vaccine timeliness, and child survival: an observational study. Lancet Glob Health.2014; 2(8): e478–87. https://doi.org/10.1016/S2214-109X(14)70274-8 PMID: 25103521

231. Wakadha H, Chandir S, Were EV, Rubin A, Obor D, Levine OS, et al. The feasibility of using mobile-phone based SMS reminders and conditional cash transfers to improve timely immunization in rural Kenya. Vaccine 2013; 31(6): 987–93. https://doi.org/10.1016/j.vaccine.2012.11.093 PMID: 23246258

232. Wallace AS, Sobel H, Ryman TK, Mantaring JB 3rd, Silvestre M, Thorley M, et al. Timing of hepatitis B vaccination and impact of non-simultaneous vaccination with DTP vaccine following introduction of a hepatitis B birth dose in the Philippines. J Public Health Policy. 2012; 33(3): 368–81. https://doi.org/10.1057/jphp.2012.18 PMID: 22673757

233. Soeung S, Thiep C, Duncan R, Patel M, Hennessey K. Using data to guide policy: next steps for preventing perinatal hepatitis B virus transmission in Cambodia. Vaccine 2012; 31(1): 149–53. https://doi.org/10.1016/j.vaccine.2012.10.079 PMID: 23127515

234. Rainey JJ, Lacapere F, Danovaro-Holliday MC, Mung K, Magloire R, Kananda G, et al. Vaccination coverage in Haiti: results from the 2009 national survey. Vaccine 2012; 30(9): 1746–51. https://doi.org/10.1016/j.vaccine.2011.12.015 PMID: 22227146

235. Poorolajal J, Khazaei S, Kousehlou Z, Bathaei S, Zahiri A. Delayed Vaccination and Related Predictors among Infants. Iran J Public Health. 2012; 41(10): 65–71. PMID: 23304664

236. Parameswaran A, Wijesinghe PR. Was there a disparity in age appropriate infant immunization uptake in the theatre of war in the North of Sri Lanka at the height of the hostilities?: a cross-sectional study in resettled areas in the Kilinochchi district. BMC Int Health Hum Rights. 2012; 12: 26. https://doi.org/10.1186/1472-698X-12-26 PMID: 23113899

237. Kapil Y, Rahul S, Rakesh K, Chinnakal P, Rai SK, Krishnan A. Significant vaccination delay can occur even in a community with very high vaccination coverage: evidence from Ballabgarh, India. J Trop Pediatr. 2012; 58(2): 133–8. https://doi.org/10.1093/tropej/fmr059 PMID: 21742766

238. Olusanya BO. Pattern and determinants of BCG immunisation delays in a sub-Saharan African community. Health Res Policy Syst. 2010; 8: 1. https://doi.org/10.1186/1478-4505-8-1 PMID: 20157426

239. Kuruvilla TA, Bridgitte A. Timing of zero dose of OPV, first dose of hepatitis B and BCG vaccines. Indian Pediatr. s 2009; 46(11): 1013–5. PMID: 19671951

240. Clark A, erson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet 2009; 373(9674): 1543–9. https://doi.org/10.1016/S0140-6736(09)60317-2 PMID: 19303633

241. Jahn A, Floyd S, Mwinuka V, Mwafilaso J, Mwagomba D, Mkisi RE, et al. Ascertainment of childhood vaccination histories in northern Malawi. Trop Med Int Health. 2008; 13(1): 129–38. https://doi.org/10.1111/j.1365-3156.2007.01982.x PMID: 18291011

242. Ndiritu M, Cowgill KD, Ismail A, Chiphatsi S, Kamau T, Fegan G, et al. Immunization coverage and risk factors for failure to immunize within the Expanded Programme on Immunization in Kenya after introduction of new Haemophilus influenzae type b and hepatitis b virus antigens. BMC Public Health. 2006; 6: 8.

243. Moisi JC, Kabuka J, Mitingi D, Levine OS, Scott JAG. Spatial and socio-demographic predictors of time-to-immunization in a rural area in Kenya: Is equity attainable? Vaccine 2010; 28(35): 5725–30. https://doi.org/10.1016/j.vaccine.2010.06.011 PMID: 20600489

244. Bicaba A, Haddad S, Kabore M, Taminy E, Feletto M, Fournier P. Monitoring the performance of the Expanded Program on Immunization: the case of Burkina Faso. BMC Int Health Hum Rights.2009; 9 Suppl 1(Suppl 1): S12. https://doi.org/10.1186/1472-698X-9-S1-S12 PMID: 19828056

245. Logullo P, Barbosa de Carvalho H, Saconi R, Massad E. Factors affecting compliance with the measles vaccination schedule in a Brazilian city. Sao Paulo Med J 2008; 126(3): 166–71. https://doi.org/10.1590/s1516-31802008000300006 PMID: 18711656

246. World Health Organization. Hepatitis B vaccines. Wkly Epidemiol Rec 2009; 84(40): 405–19. PMID: 19817017

247. Okwaraji YB, Mulholland K, Schellenberg JRMA, Andarge G, Admassu M, Edmond KM. The association between travel time to health facilities and childhood vaccine coverage in rural Ethiopia. A community based cross sectional study. BMC public health 2012; 12: 476. https://doi.org/10.1186/1471-2458-12-476 PMID: 22726457

248. Utazi CE, Thorley J, Alegana VA, Ferrari MJ, Takahashi S, Metcalf CJE, et al. Mapping vaccination coverage to explore the effects of delivery mechanisms and inform vaccination strategies. Nat Commun 2019; 10(1): 1633. https://doi.org/10.1038/s41467-019-09611-1 PMID: 30967543

249. Shet A, Carr K, Danovaro-Holliday MC, Sodha SV, Prosperi C, Wunderlich J, et al. Impact of the SARS-CoV-2 pandemic on routine immunisation services: evidence of disruption and recovery from 170 countries and territories. Lancet Glob Health. 2022; 10(2): e186–e94. https://doi.org/10.1016/S2214-109X(21)00512-X PMID: 34951973

250. Balakrishnan N, Mitra D. Left truncated and right censored Weibull data and likelihood inference with an illustration. Computational Statistics & Data Analysis 2012; 56(12): 4011–25.

Chapter 4: The burden and the spatial pattern of the various dimensions of the timeliness of childhood vaccination in The Gambia (Research Papers)

4.1 Overview of Chapter

This chapter addresses the second objective of my PhD which was; "*To describe the burden and the spatial pattern of the various dimensions of the timeliness of childhood vaccination in The Gambia*".

This chapter also tests the following hypotheses:

- *Despite an expected high overall vaccination coverage rate, various dimensions of untimely childhood vaccination, including early, delayed, and untimely intervals between doses, are likely to be prevalent in The Gambia.*
- *The prevalence of untimely vaccinations in The Gambia will demonstrate obvious subnational inequalities, with districts in the more rural regions of the country being more likely to experience higher 'un-timeliness' for all vaccines scheduled for the first year of life*.

To adequately address the second PhD objective and test the hypotheses, this chapter was divided into two research papers. The first paper was published in PLoS ONE, while the second was published in VACCINE, with the following full bibliographic information:

Wariri O, Utazi CE, Okomo U, Sogur M, Murray KA, Grundy C, Kampmann B. (2023) Timeliness of routine childhood vaccination among 12–35 months old children in The Gambia: Analysis of national immunisation survey data, 2019–2020. PLoS ONE.

Wariri O, Utazi CE, Okomo U, Metcalf CJ, Sogur M, Fofana S, Murray KA, Grundy C, Kampmann B. (2023) Mapping the timeliness of routine childhood vaccination in the Gambia: a spatial modelling study. Vaccine.

The supplementary materials, accompanying the two research papers included in this chapter are included as **Appendix 5**, **Appendix 6**, **Appendix 7** and **Appendix 8**.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1509291	**Title**	DR
First Name(s)	Oghenebrume		
Surname/Family Name	Wariri		
Thesis Title	Timeliness of routine childhood vaccination in The Gambia: examining the burden, spatial pattern, determinants and the impact of COVID-19 pandemic		
Primary Supervisor	Chris Grundy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLoS ONE		
When was the work published?	July 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?
Please list the paper's authors in the intended authorship order:

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised this study and led it's execution. I cleaned the data, merged datasets, undertook the analysis, and interpreted the results. I wrote the initial manuscript draft and handled all referencing. I handled the submission, the reviewer responses, and the re-submisison process.

SECTION E

Student Signature	[redacted]
Date	20th February 2024

Supervisor Signature	Chris Grundy
Date	21 Feb 2024

PLOS ONE

RESEARCH ARTICLE

Timeliness of routine childhood vaccination among 12–35 months old children in The Gambia: Analysis of national immunisation survey data, 2019–2020

Oghenebrume Wariri[1,2,3]*, Chigozie Edson Utazi[4,5], Uduak Okomo[1,6], Malick Sogur[7], Kris A. Murray[8], Chris Grundy[2], Sidat Fofanna[7], Beate Kampmann[1,9]

1 Vaccines and Immunity Theme, MRC Unit The Gambia at London School of Hygiene and Tropical Medicine, Fajara, The Gambia, **2** Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom, **3** Vaccine Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom, **4** WorldPop, School of Geography and Environmental Science, University of Southampton, Southampton, United Kingdom, **5** Southampton Statistical Sciences Research Institute, University of Southampton, Southampton, United Kingdom, **6** MARCH Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom, **7** Expanded Programme on Immunization, Ministry of Health and Social Welfare, Banjul, The Gambia, **8** Centre on Climate Change and Planetary Health, MRC Unit The London School of Hygiene and Tropical Medicine, Fajara, The Gambia, **9** Centre for Global Health, Charite Universitatsmedizin Berlin, Berlin, Germany

* Oghenebrume.Wariri@lshtm.ac.uk

OPEN ACCESS

Citation: Wariri O, Utazi CE, Okomo U, Sogur M, Murray KA, Grundy C, et al. (2023) Timeliness of routine childhood vaccination among 12–35 months old children in The Gambia: Analysis of national immunisation survey data, 2019–2020. PLoS ONE 18(7): e0288741. https://doi.org/10.1371/journal.pone.0288741

Editor: Orvalho Augusto, University of Washington, UNITED STATES

Received: February 22, 2023

Accepted: July 3, 2023

Published: July 21, 2023

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0288741

Data Availability Statement: The data underlying the results presented in this study were collected as part of the Gambia Demographic and Health

Abstract

The Gambia's routine childhood vaccination programme is highly successful, however, many vaccinations are delayed, with potential implications for disease outbreaks. We adopted a multi-dimensional approach to determine the timeliness of vaccination (i.e., timely, early, delayed, and untimely interval vaccination). We utilised data for 3,248 children from The Gambia 2019–2020 Demographic and Health Survey. Nine tracer vaccines administered at birth and at two, three, four, and nine months of life were included. Timeliness was defined according to the recommended national vaccination windows and reported as both categorical and continuous variables. Routine coverage was high (above 90%), but also a high rate of untimely vaccination. First-dose pentavalent vaccine (PENTA1) and oral polio vaccine (OPV1) had the highest timely coverage that ranged from 71.8% (95% CI = 68.7–74.8%) to 74.4% (95% CI = 71.7–77.1%). Delayed vaccination was the commonest dimension of untimely vaccination and ranged from 17.5% (95% CI = 14.5–20.4%) to 91.1% (95% CI = 88.9–93.4%), with median delays ranging from 11 days (IQR = 5, 19.5 days) to 28 days (IQR = 11, 57 days) across all vaccines. The birth-dose of Hepatitis B vaccine had the highest delay and this was more common in the 24–35 months age group (91.1% [95% CI = 88.9–93.4%], median delays = 17 days [IQR = 10, 28 days]) compared to the 12–23 months age-group (84.9% [95% CI = 81.9–87.9%], median delays = 16 days [IQR = 9, 26 days]). Early vaccination was the least common and ranged from 4.9% (95% CI = 3.2–6.7%) to 10.7% (95% CI = 8.3–13.1%) for all vaccines. The Gambia's childhood immunization system requires urgent implementation of effective strategies to reduce

Survey (DHS) conducted in 2019-2020. This data is publicly available for download from the DHS Program website at https://dhsprogram.com/data/available-datasets.cfm, however, it is important to note that prior permission from the DHS program must be obtained before accessing the data.

Funding: Funding This project is part of the EDCTP2 Programme supported by the European and Developing Countries Clinical Trials Partnership (grant number TMA2019CDF-2734 – TIMELY). OW was also supported by an Imperial College London Wellcome Trust Institutional Strategic Support Fund (ISSF) (grant no RSRO_P67869). CEU was supported by funding from the Bill & Melinda Gates Foundation (Investment ID INV-003287). The Vaccines and Immunity Theme (OW, UO, and BK) is jointly funded by the UK MRC and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 Programme supported by the EU (MC UP_A900/1122, MC UP A900/115). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

untimely vaccination in order to optimize its quality, even though it already has impressive coverage rates.

Introduction

The Gambian routine childhood vaccination programme is highly successful; for over a decade, it has consistently maintained routine childhood vaccination coverage rates of at least 90% for most routine childhood vaccines [1, 2]. The Gambia is therefore considered a model for the delivery and of coverage of routine childhood vaccines for many sub-Saharan African countries. The country achieved the 2020 Global Vaccine Action Plan (GVAP) coverage target a decade early [1], and is on track to reach the coverage target of the 2030 immunization agenda (IA2030) which aims to achieve at least 90% coverage for routine childhood vaccines [3]. Despite the celebrated success, there is growing evidence that many children are not receiving their vaccines within the recommended time frames [4–6]. This is particularly worrying as in parts of The Gambia, there has been a recent upsurge of measles, with a 6-fold increase in cases as of mid-2022 compared to 2020 figures despite a high coverage of both doses of measles-containing vaccine (MCV1 and MCV2) [7, 8]. Measles outbreaks are considered a sensitive marker of emerging herd immunity gaps [9] that might be created by untimely vaccination even in populations with otherwise high routine measles vaccination coverage rates [10].

Timely vaccination, operationally defined as vaccination received within the recommended age windows (i.e., valid doses) [11, 12], explores the quality dimension of immunization programs and is important for EPI programs like The Gambia that have already achieved high overage rates for most vaccines [13]. Deciding the appropriate window for childhood vaccination depends on several factors such as local disease epidemiology, presence of maternal antibodies, and the earliest age at which vaccines can be safely administered with maximum efficacy and the lowest risk of adverse effects [14]. Early vaccination, i.e., vaccines received before the earliest recommended window, may result in suboptimal immune response as maternal antibodies may inhibit vaccine response [14–18]. Conversely, delayed vaccination, i.e., vaccination received after the latest recommended window, prolongs the exposure of children to potentially life-threatening but vaccine-preventable diseases (VPDs) such as pertussis and measles [14, 19]. There are reports from other settings showing that measles outbreaks have occurred despite high vaccination coverage rates, suggesting a link to untimely vaccination [20]. Furthermore, delayed vaccination may have a domino effect on timeliness of other routine vaccines resulting in a child not completing their required vaccinations or receiving successive doses of a multi-series vaccine in an untimely manner (i.e., untimely interval vaccination) [21].

At the programmatic level, vaccinations given too early (before their earliest recommended window) or that are delayed (after the recommended windows) are key indicators for monitoring and evaluating the quality of an immunization program [22]. Untimely vaccination could be the only early warning signal that may alert the immunization system to potential problems with the delivery and uptake of vaccines. Timeliness of vaccination also has implications for the introduction of novel vaccines. For example, the World Health Organization (WHO) initially placed a strict age limit on the administration of rotavirus vaccine, stating it should not be initiated in infants aged 12 weeks or older to minimize the potential risk of intussusception, a rare form of bowel obstruction [23]. This policy restricted rotavirus vaccine introduction in many low-and middle-income countries (LMICs) where untimely vaccination was a main concern [24].

Studies exploring childhood vaccination timeliness in LMICs have gained momentum in the last decade [25]. In The Gambia, three studies, published in 2014 [6], 2015 [5], and 2016 [4] have so far assessed childhood vaccination timeliness. Nevertheless, many of the studies from LMICs, including the Gambian studies have key methodological issues that limit their utility and comparability. First, previous studies have primarily focused on delayed vaccination, with limited research into other crucial dimensions such as early vaccination and untimely interval vaccination for multi-series vaccines [25]. This one-dimensional approach provides inadequate data needed to gain a holistic understanding of untimely vaccination. Second, most of the previous studies operationalized vaccination timeliness as a categorical variable, mainly reporting the proportion of children with untimely vaccination [25]. While this approach appears pragmatic, it is simplistic, lumping together a wide window of untimely vaccinations and preventing a nuanced interpretation of the outcome. Populations with comparatively longer mean or median number of days children were vaccinated too early or delayed, outside the recommended windows, potentially have a higher likelihood of suboptimal immune response or risk of VPD outbreaks. Third, previous studies did not compare vaccination timeliness to official national routine vaccination coverage rates. Lastly, none of the Gambian studies used a nationally representative data; consequently, their findings give an incomplete picture of the true scale of untimely vaccination in The Gambia. This study, therefore, aims to bridge all the identified gaps by utilizing nationally-representative data to comprehensively investigate all dimensions of routine childhood vaccination timeliness and present categorical and continuous outcomes across two birth cohorts in The Gambia.

Materials and methods

Study setting and context

The Gambia is located in West Africa, with a population of about 2.5 million people and a birth cohort of 90,000 children who are added to the routine childhood immunization program yearly [26]. The national expanded programme on immunization (EPI) was launched in May 1979 and initially delivered six vaccines targeting tuberculosis (BCG vaccine), diphtheria, pertussis, tetanus (combined DTP vaccine), measles, polio, and yellow fever. The current childhood vaccination schedule include vaccines administered at birth and at two, three, four, nine, twelve and eighteen months of life (Table 1) [27]. We explored the timeliness of vaccination using tracer vaccines given in the first year of life, a period when the peaks and severity of VPDs are highest. The included vaccines are Bacilli Calmette Guerin (BCG) and the birth dose of Hepatitis B vaccine (HepB0) administered at birth; the first, second, and third doses of multi-series oral polio vaccine (OPV) and pentavalent vaccine (diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae type b) given at two, three and four months of life; and the first dose of measles containing vaccine (MCV1), which is administered at nine months in The Gambia (Table 1).

Data sources, study design and population

We analysed vaccination data from The Gambia Demographic and Health Survey (DHS), 2019–2020. The DHS is a nationally representative household survey that was designed by the global DHS program and implemented by the Gambia Bureau of Statistics (GBoS) [30]. The design, and implementation of the DHS is described in detail elsewhere [30]. In brief, The Gambia DHS 2019–2020 was performed using a two-stage cluster sampling design. In the first stage, the DHS selected a random sample of clusters with a probability proportional to their size within each sampling stratum from an already existing sample frame that was based on an updated version of the 2013 Gambia Population and Housing Census. In the second stage,

Table 1. The Gambia routine childhood immunization schedule showing vaccines given during infancy and the accepted national vaccination window [27].

Vaccine	Vaccination window (Timely or age-appropriate vaccination)	Early vaccination	Delayed vaccination
Hepatitis B vaccine birth dose (HepB0)*	Birth	NA	> 24 hours of life [28]
Bacilli Calmette Guerin (BCG)*		NA	> 7 days [29]
Oral Polio Vaccine (OPV0)			
Oral Polio Vaccine (OPV1)*	2 Months (61–90 days)	<61 days	>90 days
Pentavalent vaccine (PENTA1)*		<61 days	>90 days
Pneumococcal vaccine (PCV1)			
Rotavirus vaccine (Rota1)			
Oral Polio Vaccine (OPV2)*	3 Months (91–120 days)	<91 days	>120 days
Pentavalent vaccine (PENTA2)*		<91 days	>120 days
Pneumococcal vaccine (PCV2)			
Rotavirus vaccine (Rota2)			
Oral Polio Vaccine (OPV3)*	4 Months (121–150 days)	<121 days	>150 days
Pentavalent vaccine (PENTA3)*		<121 days	>150 days
Pneumococcal vaccine (PCV3)			
Inactivated Polio Vaccine (IPV)			
Measles and Rubella vaccine (MCV1)*	9 Months (271–300 days)	<271 days	>300 days
Oral Polio Vaccine (OPV4)			
Yellow Fever vaccine			
OPV1 –OPV2; OPV2 –OPV3 interval*	4–8 weeks (28–56 days)	<4 weeks or 28 days**	>8 weeks or 56 days**
PENTA1 –PENTA2; PENTA2 –PENTA3 interval*	4–8 weeks (28–56 days)	<4 weeks or 28 days**	>8 weeks or 56 days**

Note: *The tracer vaccines and vaccination intervals examined in this study. ** untimely interval represents the combination of both scenarios. Pentavalent vaccine = DPT-HepB-Hib.

https://doi.org/10.1371/journal.pone.0288741.t001

households were systematically sampled from each cluster. The samples were stratified by urban and rural areas and sample weights were determined that must be applied to generate statistics that are representative at the national, urban and rural levels, and at the Local Government Area levels (i.e., first administrative area). The Gambia DHS 2019–2020 was conducted from 21 November 2019 to 30 March 2020 in 7025 selected households [30].

The Gambia DHS 2019–2020 collected childhood immunization data from 5,148 children aged 0–35 months who received specific vaccines at any time before the survey based on information from the child's health card or the mother's recall of vaccination. Overall, 93% of the included children (0–35 months) had vaccination cards, thus, accurate information on date of birth, vaccines received, and the dates of receipt (the variables needed to compute vaccination timeliness) were extracted directly from these cards. To ensure our timeliness analyses were comparable to the routine childhood coverage estimates routinely published in the DHS final reports [30], we generated timeliness output for the 3,248 children across two age groups: 12–23 months; and 24–35 months. A comprehensive breakdown detailing the number of children in the included age group and the availability of their birth and vaccination dates for the calculation of vaccination timeliness can be found in the supporting information (S1 Table).

Measuring the dimensions of vaccination timeliness

At the individual level, we used the difference between vaccination dates and birth date to determine the age at vaccination (in days) for every vaccine. Using the nationally accepted childhood vaccination window in The Gambia (Table 1) [27], we converted the accepted age recommendations given in months and weeks to days. To ensure uniformity and

comparability, we considered a month to be equal to 30 days and a week was equal to 7 days. We considered each recommended age to begin at the first day of the window and end at the greatest number of days that could compose the given number of months or weeks (Table 1). For example, for vaccines that are recommended at two months of life, ***timely vaccination*** (or "on time") was any dose received between 61 days (the first day the child turned two months) and 90 days (the last day the child was two months). Any vaccination administered outside of the accepted window was considered "untimely" and include the following dimensions; early vaccination, delayed vaccination and untimely interval vaccination.

Early vaccination. This was defined as vaccines received *before the earliest* nationally accepted valid ages or vaccination window (in days) for a specific vaccine in The Gambia (Table 1). Since BCG and HepB0 are recommended at birth, they can either be timely or delayed and cannot be administered too early unlike the other tracer vaccines.

Delayed vaccination. This was defined as vaccines received *after the latest* nationally accepted valid ages or vaccination window (in days) for a specific vaccine in The Gambia (Table 1). The WHO recommends that infants receive HepB0 as soon as possible after birth, preferably within 24 hours [28], thus, delayed HepB0 was defined as doses received after 24 hours of life (i.e., 2 days and above). For BCG which is also recommended to be given "as soon as possible after birth", we instead used The Gambia Ministry of Health's definition of BCG received after 7 days (one week) as delayed [29].

Untimely interval vaccination. In line with the WHO guideline [31], the recommended interval for subsequent doses of multi-series vaccine in The Gambia is 4–8 weeks (i.e., 28–56 days). Thus, we defined "untimely interval vaccination" as any subsequent dose of a multi-series vaccine received before or after the recommended window (i.e., interval $<$28 days or $>$56 days between doses).

Data analysis

Following the DHS direct survey methodology, we computed routine vaccination coverage as the proportion of all eligible children (i.e., 12–23 months and 24–35 months) who were vaccinated. The denominator for computing routine vaccination coverage was all eligible children, within the specified age ranges (12–23 months and 24–35 months), with any form of vaccination evidence (i.e., either vaccination cards or mother's recall).We subsequently computed vaccination timeliness (timely, early, delayed and untimely interval vaccination) among those who were vaccinated. The denominator for computing vaccination timeliness (timely, early, delayed and untimely interval vaccination) was all eligible children whose date of birth was known, were within the specified age ranges, and whose vaccination dates were available from a vaccination card [12]. We report the proportion vaccinated (coverage, timely, and untimely vaccination) and 95% confidence interval (CI). We also computed vaccination timeliness as continuous variables and reported the median days (and interquartile range) outside the accepted window that children were vaccinated too early or too late (delayed). In all statistical analyses, we accounted for survey design and sample weights following standardized techniques [32], implemented using the *survey package* in R [33]. All analyses were performed in Rand figures were generated using the ggplot2 package [34].

Ethics

This study was based on the analysis of the openly available The Gambia demographic and health survey 2019/2020 (GDHS 2019–2020). The ethical procedures for GDHS 2019–2020 were the responsibilities of the institutions that commissioned, funded or managed the surveys. The DHS states that it sought written informed consent from all participants before data

collection and the study did not include minors. We received formal approval from the DHS program to use GDHS 2019–2020 dataset. The Gambia Government and MRC Unit The Gambia at LSHTM Joint Ethics Committee granted ethical approval for secondary data analysis (Project ID/Ethics ref: 22786; Date: 16 January, 2021).

Results

Pattern of routine vaccination coverage compared to timely vaccination

The routine vaccination coverage was high (90% or more) across all tracer vaccines. However, many children were vaccinated outside the recommended national vaccination windows as shown in the cumulative routine vaccination coverage curve in Fig 1.

Fig 2 shows the comparison between routine coverage and timely vaccination coverage in The Gambia. Overall, the coverages of all the included childhood vaccines were above 90% in the two age groups, except the coverage of OPV3 which was 88% (95% CI = 85.7–90.2) in the 24–35 months age group.

The percentage of children with timely or "on time" vaccination was higher in the 12–23 months compared to the 24–35 months age group. Timely vaccination ranged from 15.1% (95% CI = 12.1–18.1%) to 74.4% (95% CI = 71.7–77.1%) in the 12–23 months age group compared to 8.9% (95% CI = 6.6–11.1%) to 71.9% (95% CI = 68.8–75.0%) in the 24–35 months age group (Fig 1). For specific childhood vaccines, timely vaccination was lowest for the vaccines scheduled to be administered at birth, especially HepB0 and the pattern was similar in the 12–23 and 24–35 age group. Timely vaccination was highest for the vaccines scheduled to be administered at two months of life (OPV1 and Penta1), which corresponds to the next contact with the vaccination system outside the birth period (Fig 2).

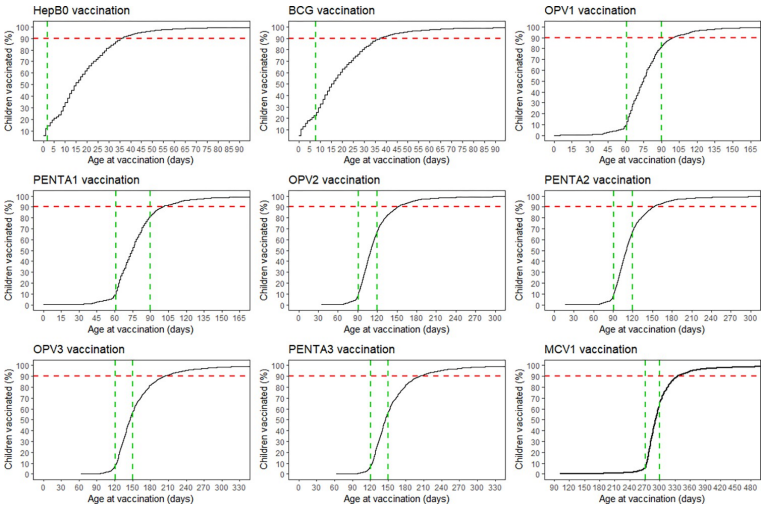


Fig 1. Cumulative routine vaccination coverage curve of children 12–35 months in The Gambia. ***Note***: Green vertical dotted lines indicate the recommended national vaccination windows (≤24 hours for HepB0, 1–7 days for BCG, 61–90 days for OPV1 and PENTA1, 91–120 days for OPV2 and PENTA2, 121–150 days for OPV3 and PENTA3, and 271–300 days for MCV1). Red dotted line indicates WHO routine vaccination coverage target. Denominator is all eligible children with any evidence of vaccination, including vaccination cards and maternal recall.

https://doi.org/10.1371/journal.pone.0288741.g001

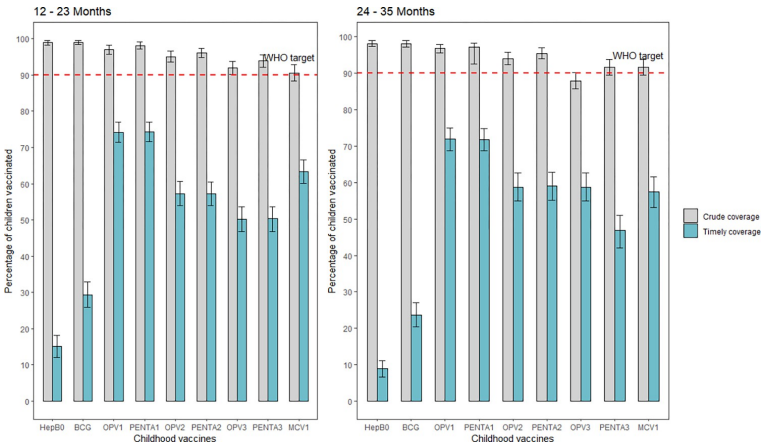


Fig 2. The comparison between routine vaccination coverage and timely vaccination coverage in The Gambia. ***Note***: Red horizontal dotted lines indicate the 2020 Global Vaccine Plan (GVAP) and the Immunization Agenda 2030 (IA2030) country-level crude vaccination coverage target. Error bar indicates 95% confidence interval (CI).

https://doi.org/10.1371/journal.pone.0288741.g002

Early vaccination (categorical and continuous outcomes)

The proportion of children who received their vaccinations too early was lower compared delayed vaccination. Overall, early vaccination ranged from 4.9% (95% CI = 3.2–6.7) to 10.7% (95% CI = 8.3–13.1) and the proportions were similar in the two age group (Fig 3A). The median number of days children were vaccinated too early, before the recommended window ranged from 3 days (IQR = 1, 11 days) to 14.5 days (IQR = 6.75, 26.25 days) and has a similar pattern in the two age groups (Fig 3B, supporting information [S2 Table]).

As per specific vaccines, the percentage of children with early vaccination was lowest for the vaccine that protect against measles infection, MCV1 (5.1% vs 4.9% in the 12–23 and 24–35 months age groups respectively). However, MCV1 had the highest median number of days that children were vaccinated too early (14.5 days, [IQR = 6.75, 26.25] and 9.0 days, [IQR = 4.0, 26.0] for 12–23 and 24–35 months age group respectively) compared to other vaccines (Fig 3B).OPV2 (in the 12–23 months) and OPV1 (in the 23–35 months) had the highest proportion of children with early vaccination representing 10.7% (95% CI = 8.3–13.1) and 10.6% (95% CI = 8.4–12.8), respectively (Fig 3A).

Delayed vaccination (categorical and continuous outcomes)

Delayed vaccination ranged from 17.5% (95% CI = 14.5–20.4) to 91.1% (95% CI = 88.9–93.4), showing a similar pattern in the two age groups (Fig 4A). The median number of days children were vaccinated too late (i.e., delayed) ranged from 11 days (IQR = 5, 19.5 days) to 28 days (IQR = 11, 57 days) across all vaccines and had a similar pattern in the two age groups (Fig 4B, supporting information [S2 Table]). Overall, HepB0 had the highest proportion of delayed vaccination across the two age groups. Specifically, delayed HepB0 was higher in the 24–35 months age group (91.1% [95% CI = 88.9–93.4], median days delayed = 17 days [IQR = 10, 28 days]) compared to the 12–23 months age group (84.9% [95% CI = 81.9–87.9], median days delayed = 16 days [IQR = 9, 26 days]).

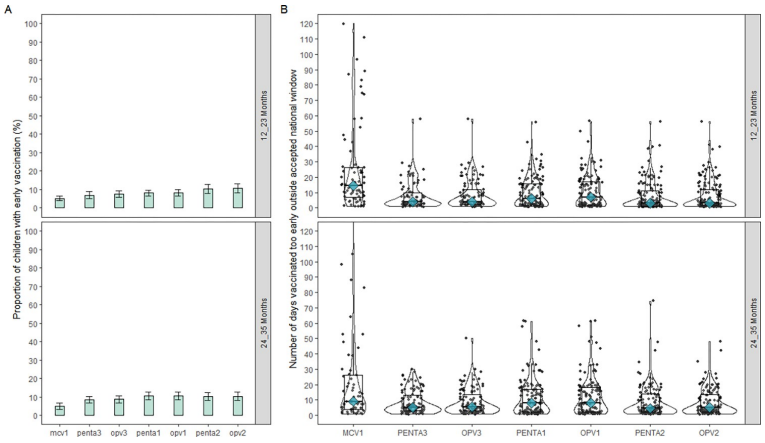


Fig 3. Early vaccination among children 12–23 months and 24–35 months in The Gambia (a) the proportion with early vaccination (categorical timeliness), (b) Number of days before the earliest accepted window that children were vaccinated too early (continuous timeliness). Note: Panel B is truncated at 120 days, thus, does not show the number of days outside the window for the outliers.

https://doi.org/10.1371/journal.pone.0288741.g003

The percentage of children with delayed vaccination was lowest for the first dose of the multi-series vaccines (i.e., OPV1 and Penta1), with a gradual increase in delayed vaccination with subsequent doses in the series across the two age groups (Fig 4A). Similarly, the median number of days that children were vaccinated too late for OPV1 in the 24–35 months age group increased from 11 days (IQR = 4, 29 days) until it peaked at 28 days (IQR = 11, 57 days) for OPV3 (Fig 4B, supporting information [S2 Table]). The 12–23 months age group also

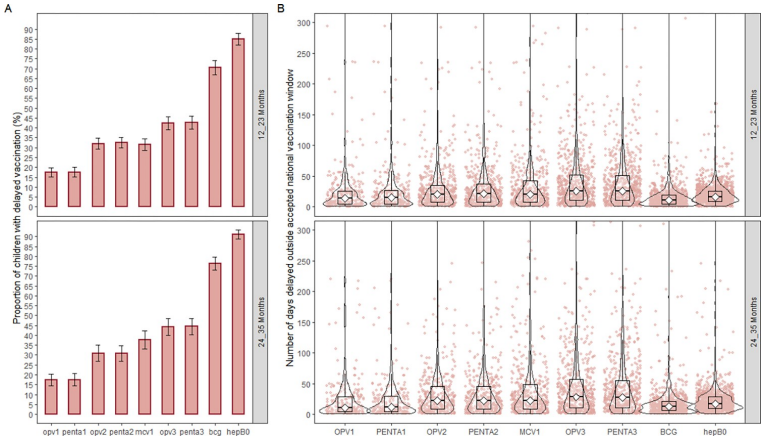


Fig 4. Delayed vaccination among children 12–23 months and 24–35 months in The Gambia (a) the proportion with delayed vaccination (categorical timeliness), (b) Number of days after the latest accepted window that children were vaccinated too late or delayed (continuous timeliness). Panel B is truncated at 300 days, thus, does not show the number of days outside the window for the outliers.

https://doi.org/10.1371/journal.pone.0288741.g004

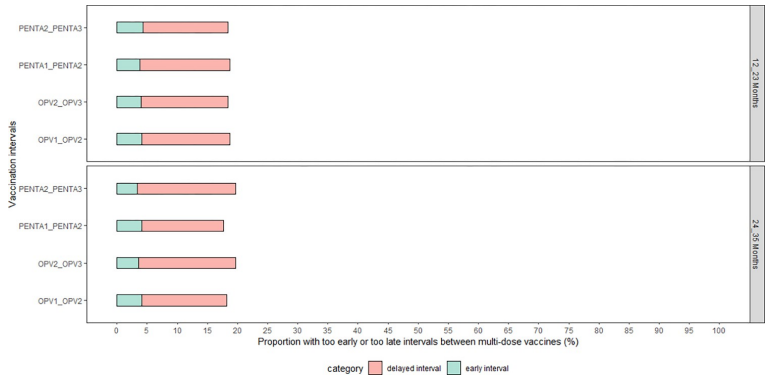


Fig 5. The proportion of children with untimely interval vaccination for subsequent doses of multi-series vaccines in The Gambia. Note: continuous timeliness (number of days outside the interval) was not computed for this dimension of vaccination timeliness because "untimely interval" include those who were vaccinated before and after the recommended interval for the multi-series vaccines.

https://doi.org/10.1371/journal.pone.0288741.g005

followed a similar pattern of increasing median days children were vaccinated too late with subsequent doses of the multi-series vaccines.

Untimely interval of vaccination between multi-series vaccines

Overall, less than 20% of the vaccinated children received their multi-series vaccines outside of the recommended window (i.e., a minimum interval of four weeks and maximum interval of eight weeks between subsequent doses of multi-series vaccines). This trend was observed consistently across both age cohorts and across all multi-series vaccines (Fig 5). Too early interval (i.e., being vaccinated less than 4 weeks or 28 days between subsequent doses of multi-series vaccines) was the least common, accounting for less than 5% for all multi-series vaccines (Fig 5).

Discussion

To the best of our knowledge, this is the first study conducted in an LMIC context to simultaneously investigate all the dimensions of vaccination timeliness (timely, early, delayed, and untimely interval), and presents the outcomes as both categorical and continuous variables. This approach allows for a uniquely nuanced interpretation of the results unlike previous studies that often focused on one dimension or predominantly reported the outcomes as categorical variables. We also compared vaccination timeliness to official national survey-based routine vaccination coverage rates. Although overall coverage was high, a large number of children were vaccinated outside the recommended time-frames. Early vaccination was the least common dimension of untimely vaccination and also had a comparatively shorter median number of days children were vaccinated outside the window. Delayed vaccination was the most common dimension of untimely vaccination, with the highest proportion and longest median number of days children were vaccinated outside the recommended time-frames. Our findings do not align with prior research on vaccination timeliness, as the proportion of delayed vaccinations and the median delays in our study are generally lower compared to the largest study so far that included data of 217,706 children from 45 LMICs [35]. Our findings demonstrate that the Gambia EPI not only achieves high routine childhood vaccination

coverage rates but has also ensured that children receive their vaccinations within the recommended time-frames, as much as possible, in comparison to other LMICs.

In the last decade, The Gambian EPI program has further strengthened its commitment to leave no child behind and to reach 100% immunization coverage in the country. This commitment is supported by development partners such as Gavi, the Vaccine Alliance which continues to make huge investments towards ensuring that all children receive all their basic vaccinations within the recommended time-frames [36]. These commitments and investments might explain why vaccination was generally more timely in the younger age group (12–23 months) compared to children in the older age group. This improvement in timely vaccination is similar to the official national survey-based routine vaccination coverage estimates which shows that coverage was also higher among children in the younger age group [30].

For the multi-series vaccines, the proportion and median delays increased gradually and peaked with the third doses, reflecting a pattern similar to previous studies from Indonesia [37], the UK [38], and across LMICs context [35]. This trend is not surprising because the first doses of the multi-series vaccines are administered at two months of life in The Gambia which coincides with the first vaccination visit outside the birth period and may also be an opportunity to receive post-natal services, hence, the timely uptake. Nevertheless, it is worrisome because it reflects the inability of the program to consistently ensure timely vaccination or a lack of enthusiasm by caregivers for subsequent doses of multi-series vaccines. This situation may have a knock-on effect as many children may progress from untimely vaccination in subsequent doses to actual dropout from the system with increasing median delays with subsequent doses. Our results should, therefore, inform the development of retention strategies by the EPI for multi-series vaccines aimed at delivering doses in a timely manner.

Implications for childhood vaccination planning and policy in The Gambia

The fact that HepB0 had the highest proportion (∼90%) and median delay of more than two weeks in both age groups is of particular concern and has implication for immunization planning and public health policy. Globally, about 360 million people are chronically infected with Hepatitis B virus (HBV) and can lead to serious complications such as liver cirrhosis or cancer [28]. In The Gambia, HBV infection is endemic, with 15% to 20% of the population being chronically infected [39]. HBV can be transmitted from mother-to-child during the birthing process and through breast feeding. Thus, the WHO has recommended that HepB0, one of the safest and most effective vaccines, be given within 24 hours of birth and followed by at least two subsequent doses to prevent perinatal infection [28]. The ∼90% delay found in this study is an improvement compared to the 98.9% HepB0 delay recorded in the Gambia in 2015 [4]. However, it highlights the need for more action to ensure timely delivery and uptake of HepB0 in the country. The evidence base suggests that the key drivers of delayed HepB0 are lack of facility delivery or mothers being discharged before their babies can be accessed for vaccination [40, 41]. While these drivers might not be under the direct purview of the EPI, the programme can work collaboratively with the relevant department of the ministry health to better align priorities.

The fact that the categorical measures of vaccination timeliness showed a contrasting pattern to the continuous measures of timeliness for most vaccines, highlights the need for studies to operationalize timeliness using the two outcome measures. The subpopulation with a longer median duration of untimely (early or late) vaccination can create windows of vulnerability, even when the overall proportion of children with early or delayed vaccination is low. For this reason, it is important for EPI programs to supplement routine measures of coverage and categorical timeliness with continuous measures of vaccination timeliness to aid a nuanced

interpretation of the quality dimension of routine immunization system performance. Our findings contextualizes the available evidence in The Gambia which shows that routine vaccination coverage of MCV1 is high [2], and the proportion of children vaccinated too early for MCV1 is generally low [5], because we provide additional evidence on the median number of days children are vaccinated outside the recommended time-frames. Efforts at reducing the median number of days that children are vaccinated too early or late, in addition to increasing timely, age-appropriate MCV1 coverage and other measures must be prioritized by the Gambia EPI to halt sporadic measles outbreaks in the country.

Transferability and future research

To ensure comparability of data, future studies examining vaccination timeliness in other LMICs contexts can implement the approach we have adopted in defining the dimensions of vaccination timeliness. We acknowledge that vaccination windows may vary across countries, nevertheless, using the nationally accepted EPI vaccination windows, rather than an arbitrary definition makes it easier to aggregate and compare data across countries, especially LMICs with similar vaccination schedules. Nationally-representative surveys such as DHS and the multiple indicator cluster survey (MICS) are widely implemented in many LMICs and routinely generate national-level routine vaccination coverage rates. The widespread availability of these surveys presents an opportunity to replicate the analysis implemented in this study by comparing routine vaccination coverage rates with estimates of all the dimensions of vaccination timeliness. Through this approach, countries can monitor the quality dimension of their immunization systems, in addition to measuring routine vaccination coverage rates which can mask substantial immunity gaps created by untimely vaccinations.

To effectively implement targeted public health interventions, it might be necessary to move beyond utilizing national and subnational estimates of vaccination timeliness and instead identify specific subpopulations that are 'hotspots' of untimely vaccination. Future studies should deploy geospatial modelling techniques and generate maps showing the hotspots of early, delayed, and untimely interval vaccination at high-resolution, similar to spatial modelling of routine vaccination coverage already being conducted [42–44]. The factors that contribute to the pattern of untimely vaccination observed in this study are likely to be multifaceted and complex. In order to gain a deeper and more comprehensive understanding of these factors, future studies should adopt an action-oriented conceptual framework that takes into account both accessibility and utilization of immunization services, as well as demand- and supply-side factors. This approach will allow for a more robust examination of the various factors contributing to untimely vaccination, providing valuable insights for the development and implementation of effective strategies to improve vaccination timeliness.

Methodological implications and limitations

To compute vaccination timeliness, dates of birth and vaccination are essential, and the percentage of children with vaccination cards must be high to ensure the analysis is powered to generate representative outcomes [45]. Vaccination card availability was high in our dataset and in the age group we included (~ 85%), thus, supporting the feasibility of implementing our timeliness analysis. However, in many LMICs context, the retention of vaccination cards is variable and may limit the computation of timeliness outcomes. To conduct timeliness analysis in situations where dates of birth and vaccination are incomplete, there is a need to develop, validate, and deploy methodologies that can input or predict age at vaccination especially in situations where it can be confirmed from maternal recall that the child has been vaccinated. Such imputation or prediction techniques can utilize machine learning approaches

that may leverage pre-specified characteristics such as the age at vaccination of children in similar age bands or living in the same spatial location with the index child [35, 46].

The use of DHS data for the analyses of vaccination timeliness presents certain limitations inherent to the nature of the survey data. First, the availability of valid date of birth and date of vaccination for a substantial number of children in the dataset is crucial for accurate analysis. However, the completeness and accuracy of these data elements can vary significantly across many LMIC context where the availability of home-based vaccination records are seldom incomplete. This can potentially introduce biases or limit the generalizability of the timeliness estimates. Second, cross-sectional surveys like DHS provide a snapshot of the population at a specific point in time. Since the data is typically collected every 5 years and focusses on children who were vaccinated 12–35 months before the survey was implemented, it does not reflect the most recent vaccination status and poses challenges in capturing the temporal nature of vaccination timeliness. Locally tailored approaches are needed to generate timely, high-quality, population-based vaccination data needed to assess to temporal trends in vaccination timeliness. The availability of such real-time, routinely collected data has fundamental advantages over data generated through periodic (~5 yearly) surveys like the DHS and can be exploited in the future for the analysis implemented in this study. Despite these limitations, DHS data is a valuable resource for tracking vaccination timeliness. DHS data is collected in a standardized way across countries, which makes it possible to compare vaccination rates across countries. DHS data is also collected from a large sample of households, which makes it possible to get a reliable estimate of vaccination rates.

Supporting information

S1 Fig. Flowchart displaying children included in this study by age group and birth/vaccination data completeness.
(DOCX)

S1 Table. Median number of days children were vaccinated too early and interquartile ranges for all vaccines for children 12–23 and 24–35 months in The Gambia.
(DOCX)

S2 Table. Median delays and interquartile ranges for all vaccines for children 12–23 and 24–35 months in The Gambia.
(DOCX)

Author Contributions

Conceptualization: Oghenebrume Wariri, Chigozie Edson Utazi, Uduak Okomo, Malick Sogur, Kris A. Murray, Chris Grundy, Sidat Fofanna, Beate Kampmann.

Data curation: Oghenebrume Wariri, Chigozie Edson Utazi.

Formal analysis: Oghenebrume Wariri, Chigozie Edson Utazi.

Funding acquisition: Oghenebrume Wariri, Beate Kampmann.

Investigation: Oghenebrume Wariri, Beate Kampmann.

Methodology: Oghenebrume Wariri, Chigozie Edson Utazi, Uduak Okomo, Malick Sogur, Kris A. Murray, Chris Grundy, Sidat Fofanna, Beate Kampmann.

Project administration: Oghenebrume Wariri.

Resources: Oghenebrume Wariri, Malick Sogur.

Software: Chigozie Edson Utazi.

Supervision: Chigozie Edson Utazi, Uduak Okomo, Kris A. Murray, Chris Grundy, Sidat Fofanna, Beate Kampmann.

Validation: Oghenebrume Wariri.

Visualization: Oghenebrume Wariri, Chigozie Edson Utazi.

Writing – original draft: Oghenebrume Wariri.

Writing – review & editing: Chigozie Edson Utazi, Uduak Okomo, Malick Sogur, Kris A. Murray, Chris Grundy, Sidat Fofanna, Beate Kampmann.

References

1. Wariri O, Edem B, Nkereuwem E, et al. Tracking coverage, dropout and multidimensional equity gaps in immunisation systems in West Africa, 2000–2017. *BMJ Global Health* 2019; 4(5): e001713–e. https://doi.org/10.1136/bmjgh-2019-001713 PMID: 31565416
2. Wariri O, Nkereuwem E, Erondu NA, et al. A scorecard of progress towards measles elimination in 15 west African countries, 2001–19: a retrospective, multicountry analysis of national immunisation coverage and surveillance data. *The Lancet Global Health* 2021; 9(3): e280–e90. https://doi.org/10.1016/S2214-109X(20)30481-2 PMID: 33607028
3. World Health Organization. Implementing the Immunization Agenda 2030: A Framework for Action through Coordinated Planning, Monitoring & Evaluation, Ownership & Accountability, and Communications & Advocacy. Geneva, Switzerland: World Health Organization, 2021.
4. Miyahara R, Jasseh M, Gomez P, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. *Vaccine* 2016; 34(29): 3335–41. https://doi.org/10.1016/j.vaccine.2016.05.017 PMID: 27195759
5. Odutola A, Afolabi MO, Ogundare EO, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. *BMC health services research* 2015; 15: 346. https://doi.org/10.1186/s12913-015-1015-9 PMID: 26315547
6. Scott S, Odutola A, Mackenzie G, et al. Coverage and timing of children's vaccination: an evaluation of the expanded programme on immunisation in The Gambia. *PLoS One* 2014; 9(9): e107280. https://doi.org/10.1371/journal.pone.0107280 PMID: 25232830
7. World Health Organization. Surveillance for Vaccine Preventable Diseases (VPDs). 2022. https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance/surveillance-for-vpds (accessed 19 July 2022).
8. Sowe A, Njie M, Sowe D, et al. Epidemiology of measles cases, vaccine effectiveness, and performance towards measles elimination in The Gambia. *PLoS One* 2021; 16(10): e0258961. https://doi.org/10.1371/journal.pone.0258961 PMID: 34673828
9. Gastañaduy PA, Goodson JL, Panagiotakopoulos L, Rota PA, Orenstein WA, Patel M. Measles in the 21st Century: Progress Toward Achieving and Sustaining Elimination. *J Infect Dis* 2021; 224(12 Suppl 2): S420–s8. https://doi.org/10.1093/infdis/jiaa793 PMID: 34590128
10. Truelove SA, Graham M, Moss WJ, Metcalf CJE, Ferrari MJ, Lessler J. Characterizing the impact of spatial clustering of susceptibility for measles elimination. *Vaccine* 2019; 37(5): 732–41. https://doi.org/10.1016/j.vaccine.2018.12.012 PMID: 30579756
11. MacDonald SE, Russell ML, Liu XC, et al. Are we speaking the same language? an argument for the consistent use of terminology and definitions for childhood vaccination indicators. *Hum Vaccin Immunother* 2019; 15(3): 740–7. https://doi.org/10.1080/21645515.2018.1546526 PMID: 30457475
12. World Health Organization. Harmonizing vaccination coverage measures in household surveys: A primer. Geneva, Switzerland: WHO, 2019.
13. Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS medicine* 2013; 10(5): e1001404. https://doi.org/10.1371/journal.pmed.1001404 PMID: 23667334
14. Plotkin SA. Vaccines: Past, present and future. *Nature Medicine* 2005; 11(4S): S5–S. https://doi.org/10.1038/nm1209 PMID: 15812490
15. Nic Lochlainn LM, de Gier B, van der Maas N, et al. Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review

and meta-analysis. *The Lancet Infectious Diseases* 2019; 19(11): 1246–54. https://doi.org/10.1016/S1473-3099(19)30396-2 PMID: 31548081

16. Borràs E, Urbiztondo L, Costa J, et al. Measles antibodies and response to vaccination in children aged less than 14 months: implications for age of vaccination. *Epidemiol Infect* 2012; 140(9): 1599–606. https://doi.org/10.1017/S0950268811002184 PMID: 22074684
17. Garly ML, Balé C, Martins CL, et al. Measles antibody responses after early two dose trials in Guinea-Bissau with Edmonston-Zagreb and Schwarz standard-titre measles vaccine: better antibody increase from booster dose of the Edmonston-Zagreb vaccine. *Vaccine* 2001; 19(15–16): 1951–9. https://doi.org/10.1016/s0264-410x(00)00431-x PMID: 11228365
18. Whittle H, Hanlon P, O'Neill K, et al. Trial of high-dose Edmonston-Zagreb measles vaccine in the Gambia: antibody response and side-effects. *Lancet* 1988; 2(8615): 811–4. https://doi.org/10.1016/s0140-6736(88)92781-x PMID: 2902264
19. Guerra FA. Delays in immunization have potentially serious health consequences. Paediatr Drugs; 2007. p. 143–8. https://doi.org/10.2165/00148581-200709030-00002 PMID: 17523694
20. Henderson DA, Dunston FJ, Fedson DS, et al. The Measles Epidemic: The Problems, Barriers, and Recommendations. *JAMA* 1991; 266(11): 1547–52.
21. Kiely M, Boulianne N, Talbot D, et al. Impact of vaccine delays at the 2, 4, 6 and 12 month visits on incomplete vaccination status by 24 months of age in Quebec, Canada. *BMC Public Health* 2018; 18 (1): 1364.
22. World Health Organization. Training for mid-level managers (MLM) module 5: monitoring the immunization system. Geneva, 2008.
23. World Health O. Rotavirus vaccines: an update. *Weekly Epidemiological Record = Relevé épidémiologique hebdomadaire* 2009; 84(51–52): 533–40.
24. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. *PLoS Med* 2012; 9(10): e1001330. https://doi.org/10.1371/journal.pmed.1001330 PMID: 23109915
25. Wariri O, Okomo U, Kwarshak YK, et al. Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps. *PLOS Global Public Health* 2022; 2(7): e0000325. https://doi.org/10.1371/journal.pgph.0000325 PMID: 36962319
26. Worldometer. The Gambia Population. 2021. https://www.worldometers.info/world-population/gambia-population/ (accessed November 19 2021).
27. World Health Organization. Vaccination schedule for Gambia. 2023. https://immunizationdata.who.int/pages/schedule-by-country/gmb.html?DISEASECODE=&TARGETPOP_GENERAL= (accessed 29 January 2023).
28. World Health Organization. Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination. Geneva, Switzerland: World Health Organization, 2015.
29. Ministry of Health The Gambia. Draft policy of the expanded programme on immunisation, Republic of The Gambia. Banjul, The Gambia: Ministry of Health The Gambia, 2006.
30. Gambia Bureau of Statistics (GBoS) and ICF. The Gambia Demographic and Health Survey 2019–20. Banjul, The Gambia and Rockville, Maryland, USA, 2021.
31. World Health Organization. Summary of WHO Position Papers—Recommended Routine Immunizations for Children. Geneva, Switzerland: World Health Organization, 2020.
32. International ICF. Demographic and Health Survey Sampling and Household Listing Manual. MEASURE DHS, Calverton, Maryland, U.S.A.: ICF International, 2012.
33. Lumley T. Analysis of Complex Survey Samples. *Journal of Statistical Software* 2004; 9(8): 1–19.
34. R Core Team R. R: A language and environment for statistical computing. 2022.
35. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet* 2009; 373(9674): 1543–9. https://doi.org/10.1016/S0140-6736(09)60317-2 PMID: 19303633
36. Gavi The Vaccine Alliance. Program impact: The Gambia. 2022. https://www.gavi.org/programmes-impact/country-hub/africa/gambia (accessed 27 January 2023).
37. Oktaria V, Bines JE, Murni IK, et al. Timeliness of routine childhood vaccinations in Indonesian infants in the first year of life. *Vaccine* 2022; 40(21): 2925–32. https://doi.org/10.1016/j.vaccine.2022.04.001 PMID: 35422336

38. Walton S, Cortina-Borja M, Dezateux C, et al. Measuring the timeliness of childhood vaccinations: Using cohort data and routine health records to evaluate quality of immunisation services. *Vaccine* 2017; 35(51): 7166–73. https://doi.org/10.1016/j.vaccine.2017.10.085 PMID: 29132992

39. Kirk GD, Lesi OA, Mendy M, et al. The Gambia Liver Cancer Study: Infection with hepatitis B and C and the risk of hepatocellular carcinoma in West Africa. *Hepatology* 2004; 39(1): 211–9. https://doi.org/10.1002/hep.20027 PMID: 14752840

40. Montagu D, Yamey G, Visconti A, Harding A, Yoong J. Where Do Poor Women in Developing Countries Give Birth? A Multi-Country Analysis of Demographic and Health Survey Data. *PLOS ONE* 2011; 6(2): e17155. https://doi.org/10.1371/journal.pone.0017155 PMID: 21386886

41. Bryce J, Daelmans B, Dwivedi A, et al. Countdown to 2015 for maternal, newborn, and child survival: the 2008 report on tracking coverage of interventions. *Lancet* 2008; 371(9620): 1247–58. https://doi.org/10.1016/S0140-6736(08)60559-0 PMID: 18406859

42. Utazi CE, Nilsen K, Pannell O, Dotse-Gborgbortsi W, Tatem AJ. District-level estimation of vaccination coverage: Discrete vs continuous spatial models. *Statistics in Medicine* 2021; 40(9): 2197–211. https://doi.org/10.1002/sim.8897 PMID: 33540473

43. Dong TQ, Wakefield J. Modeling and presentation of vaccination coverage estimates using data from household surveys. *Vaccine* 2021; 39(18): 2584–94. https://doi.org/10.1016/j.vaccine.2021.03.007 PMID: 33824039

44. Utazi CE, Thorley J, Alegana VA, et al. High resolution age-structured mapping of childhood vaccination coverage in low and middle income countries. *Vaccine* 2018; 36(12): 1583–91. https://doi.org/10.1016/j.vaccine.2018.02.020 PMID: 29454519

45. Wagai JN, Rhoda D, Prier M, et al. Implementing WHO guidance on conducting and analysing vaccination coverage cluster surveys: Two examples from Nigeria. *PLoS One* 2021; 16(2): e0247415. https://doi.org/10.1371/journal.pone.0247415 PMID: 33635913

46. Li Y, Vinzamuri B, Reddy CK. Regularized weighted linear regression for high-dimensional censored data. Proceedings of the 2016 SIAM International Conference on Data Mining; 2016: SIAM; 2016. p. 45–53.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1509291	**Title**	DR
First Name(s)	Oghenebrume		
Surname/Family Name	Wariri		
Thesis Title	Timeliness of routine childhood vaccination in The Gambia: examining the burden, spatial pattern, determinants and the impact of COVID-19 pandemic		
Primary Supervisor	Chris Grundy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Vaccine		
When was the work published?	September 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?
Please list the paper's authors in the intended authorship order:

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised this study and led it's execution. I cleaned the data, merged datasets, undertook the analysis, and interpreted the results. I wrote the initial manuscript draft and handled all referencing. I handled the submission, the reviewer responses, and the re-submisison process.

SECTION E

Student Signature	[redacted]
Date	20th February 2024

Supervisor Signature	Chris Grundy
Date	21 Feb 2024

4.3 Research Paper 2 (VACCINE)

Vaccine 41 (2023) 5696–5705

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Mapping the timeliness of routine childhood vaccination in The Gambia: A spatial modelling study

Oghenebrume Wariri [a,b,c,*], Chigozie Edson Utazi [d,e], Uduak Okomo [a,f], C. Jessica E. Metcalf [g], Malick Sogur [h], Sidat Fofana [h], Kris A. Murray [i,1], Chris Grundy [b,1], Beate Kampmann [a,c,j,1]

[a] Vaccines and Immunity Theme, MRC Unit The Gambia a London School of Hygiene and Tropical Medicine, Fajara, Gambia
[b] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom
[c] Vaccine Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom
[d] WorldPop, School of Geography and Environmental Science, University of Southampton, Southampton, United Kingdom
[e] Southampton Statistical Sciences Research Institute, University of Southampton, Southampton, United Kingdom
[f] MARCH Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom
[g] Department of Ecology & Evolutionary Biology, Princeton University, Princeton, NJ, USA
[h] Expanded Programme on Immunization, Ministry of Health and Social Welfare, The Gambia, Banjul, Gambia
[i] Centre on Climate Change and Planetary Health, MRC Unit The Gambia at The London School of Hygiene and Tropical Medicine, Fajara, Gambia
[j] Centre for Global Health, Charité Universitatsmedizin, Berlin, Germany

A B S T R A C T

Introduction: Timeliness of routine vaccination shapes childhood infection risk and thus is an important public health metric. Estimates of indicators of the timeliness of vaccination are usually produced at the national or regional level, which may conceal epidemiologically relevant local heterogeneities and make it difficult to identify pockets of vulnerabilities that could benefit from targeted interventions. Here, we demonstrate the utility of geospatial modelling techniques in generating high-resolution maps of the prevalence of delayed childhood vaccination in The Gambia. To guide local immunisation policy and prioritize key interventions, we also identified the districts with a combination of high estimated prevalence and a significant population of affected infants.

Methods: We used the birth dose of the hepatitis-B vaccine (HepB0), third-dose of the pentavalent vaccine (PENTA3), and the first dose of measles-containing vaccine (MCV1) as examples to map delayed vaccination nationally at a resolution of $1 \times 1\text{-km}^2$ pixel. We utilized cluster-level childhood vaccination data from The Gambia 2019–20 Demographic and Health Survey. We adopted a fully Bayesian geostatistical model incorporating publicly available geospatial covariates to aid predictive accuracy. The model was implemented using the integrated nested Laplace approximation—stochastic partial differential equation (INLA-SPDE) approach.

Results: We found significant subnational heterogeneity in delayed HepB0, PENTA3 and MCV1 vaccinations. Specific districts in the central and eastern regions of The Gambia consistently exhibited the highest prevalence of delayed vaccination, while the coastal districts showed a lower prevalence for all three vaccines. We also found that districts in the eastern, central, as well as in coastal parts of The Gambia had a combination of high estimated prevalence of delayed HepB0, PENTA3 and MCV1 and a significant population of affected infants.

Conclusions: Our approach provides decision-makers with a valuable tool to better understand local patterns of untimely childhood vaccination and identify districts where strengthening vaccine delivery systems could have the greatest impact.

1. Introduction

Immunisation is a highly effective and cost-efficient means of controlling infectious diseases [1]. Studies estimate that every dollar spent on immunisation yields a return on investment (ROI) of more than 16 dollars. If the broader benefits of immunisation are considered, the ROI rises to 48 dollars [2]. Since its establishment, the expanded programme on immunisation (EPI) has significantly reduced the incidence of and mortality from childhood vaccine-preventable diseases (VPDs) [3]. Between 2000 and 2019, vaccination programs in low- and middle-income countries (LMICs) prevented 36 million deaths among children aged under five [4]. Despite these hard-won successes, the COVID-19 pandemic caused the biggest setback in routine childhood vaccinations in 30 years. In 2021 alone, 18.2 million children globally did not receive the first dose of the diphtheria-tetanus-pertussis (DTP) containing vaccine, and an additional 6.8 million children were under-vaccinated [5]. Thus, a more holistic approach, considering different aspects of the routine vaccination system, needs to be adopted to

* Corresponding author at: Vaccines and Immunity Theme, MRC Unit The Gambia at London School of Hygiene and Tropical Medicine, Fajara, Gambia.
E-mail address: Oghenebrume.Wariri@lshtm.ac.uk (O. Wariri).
[1] Co-senior authors.

https://doi.org/10.1016/j.vaccine.2023.08.004
Received 20 June 2023; Received in revised form 29 July 2023; Accepted 1 August 2023
Available online 8 August 2023

facilitate speedy recovery from the drastic disruptions caused by the pandemic.

The success of EPI programs has traditionally been evaluated by measuring vaccination coverage rates [6,7]. This indicator assumes uptake and overlooks whether doses are received within the recommended window, are too early or delayed [8,9]. Yet, several factors, including local VPD epidemiology, maternal antibodies, and the earliest safe age for a vaccination with optimal efficacy and minimal risks, determine an ideal age window for vaccination [10]. High coverage and timely delivery are crucial to achieve the full benefits of vaccines [6]. Timely vaccination, that is, vaccination received within the recommended window in an age-appropriate manner [11], is an essential quality dimension of immunisation programs for various reasons. At the programmatic level, too early or delayed vaccination could alert program managers to potential issues with vaccine delivery [7]. At the individual level, vaccines received too early could lead to suboptimal immune response due to interference with maternal antibodies [12,13]. Conversely, delayed vaccination could increase children's exposure to VPDs, such as pertussis and measles, whose peaks occur during the first year of life [10,14]. Because of its high infectivity rate, measles requires at least 95 % vaccination coverage and population immunity to prevent outbreaks [15]. However, evidence from high-income countries suggests that measles outbreaks have occurred in the past due to suboptimal population immunity associated with delayed measles vaccination, even in the presence of a high overall coverage [16]. It is therefore imperative that countries like The Gambia [17,18], which have attained a persistently high vaccination coverage, must now explore the quality dimension – i.e., ensuring that children across all subpopulations receive vaccination in a timely, age-appropriate manner.

Regardless of source or strength of evidence of vaccination, survey-based estimates of vaccination coverage are typically produced at the national level or at the scale of large regions. This approach is often due to administrative convenience, operational limitations, or high cost of data collection to produce more spatially detailed estimates. Such large-area estimates mask epidemiologically important heterogeneities in local vaccine coverage and limit the identification of low coverage areas capable of sustaining pockets of disease transmission and which could benefit from targeted efforts [19]. Consequently, geospatial modelling approaches, utilizing geolocated household survey data have gained traction as a vital tool for creating high-resolution estimates and maps of vaccination coverage [20–24]. Recently, studies exploring the timeliness of childhood vaccination in LMICs have also gained significant momentum [25,26]. Nevertheless, to date, no studies have produced high-resolution maps showing the spatial patterns of the timeliness of routine childhood vaccination. The Immunization Agenda 2030 (IA2030) is an ambitious global strategy that aims to halve the number of under- or unvaccinated children and eliminate measles transmission globally [3]. This requires new data and methodological approaches to precisely locate and target these subpopulations to ensure no one is left behind. Maps are a powerful tool that can help identify vulnerable subpopulations and their programmatic relevance in vaccination is well recognised by the WHO IA2030 [3], UNICEF, and Gavi, the Vaccine Alliance [27].

In this paper, we show the utility of geospatial modelling techniques for high-resolution mapping of the timeliness of routine vaccination in The Gambia. We mapped the prevalence of delayed vaccination nationally at 1 × 1-km^2 resolution, second (District), and third (Wards) health administrative levels among children aged 12–35 months in The Gambia. To guide immunisation micro-planning, we also identified the specific districts and wards where there was a combination of high estimated prevalence and a significant population of affected infants. We focused our spatial analysis on delayed vaccination because we have previously shown that it is significantly more prevalent in The Gambia than other dimensions of vaccination timeliness [28]. We used the birth-dose of hepatitis-B vaccine (HepB0), the third dose of pentavalent vaccine (PENTA3) and the first-dose of the measles-containing vaccine (MCV1) as case studies for three reasons. First, several studies have shown that delayed HepB0 is a key marker of incomplete or delayed subsequent doses of routinely recommended childhood vaccines [29,30]. Second, the coverage of PENTA3 (formerly coverage of DPT3) is commonly used as a performance indicator for routine vaccine delivery in The Gambia and globally [7]. Third, a single valid dose of a measles-containing vaccine is approximately 93 % effective in providing lifelong protection against measles [31]. Yet, despite achieving consistently high coverage of MCV1, The Gambia experienced a significant six-fold increase in measles cases by mid-2022 compared to the numbers reported in 2020 [32]. Postponed measles campaigns and stagnating MCV1 coverage since 2017, along with the potential impact of delayed MCV1 resulting in the accumulation of susceptible sub-populations, might explain the recent trend. The high-resolution geospatial mapping of delayed HepB0, PENTA3 and MCV1 may therefore offer critical insights on the pattern of vaccination timeliness that could guide targeted programmatic actions in The Gambia and serve as an example for other immunisation programs.

2. Methods

2.1. Study setting and context

The Gambia, situated in West Africa, has a population of 2.5 million and a yearly birth cohort of about 90,000 children who are added to the routine childhood immunisation program [33]. In May 1967, The Gambia achieved the distinction of being the first country in the world to interrupt the transmission of measles virus successfully [34]. The Gambian EPI was established in 1979 with six vaccines targeting tuberculosis (BCG vaccine), diphtheria, pertussis, tetanus (combined DTP vaccine), measles, polio, and yellow fever. The current vaccination schedule includes several additional vaccines recommended at birth, two, three, four, nine, twelve and eighteen months of age [35].

2.2. Data collection

We obtained cluster-level routine vaccination data for HepB0, PENTA3 and MCV1 for children aged 12–35 months from the 2019–20 Gambia Demographic and Health Survey (GDHS) [36]. The GDHS used a stratified, two-stage sampling design to produce estimates of health and demographic indicators, including vaccination coverage at the national and Local Government Area (LGA) levels and for urban and rural areas. Stratification was achieved by separating each of the eight LGAs (i.e., Banjul, Basse, Brikama, Janjanbureh, Kanifing, Kerewan, Kuntaur and Mansakonko) into urban and rural areas [36]. Samples were drawn from within each stratum in two stages. In the first stage, survey clusters were selected using a probability proportional to their size within each sampling stratum from a national sampling frame. In the second stage, households were randomly selected from household lists within the chosen clusters. The survey was implemented in a total of 281 clusters and 7,025 selected households between 21 November 2019 to 30 March 2020 [36].

The 2019–20 GDHS collected childhood immunization data from 5,148 children aged 0–35 months who received vaccines at any time before the survey. The data was collected based on the mother's recall of vaccination or parent-held vaccination cards. However, to determine the timeliness of vaccination, we require a child's date of birth and vaccination dates [6], information only available from their home-based vaccination records (HBR). We therefore restricted our analysis to the 3,248 children (93 % of 12–35-month-olds) with complete birth and vaccination dates from their home-based vaccination records. For each child, we also extracted the geographical locations, i.e., latitude and longitude of the cluster from which their household was selected.

2.3. Defining and computing vaccination timeliness

We used the accepted childhood vaccination window for The Gambia [35], converting age recommendations from months to days. For consistency, we considered a month to be 30 days. Delayed HepB0, PENTA3 or MCV1 was defined as being vaccinated after the latest recommended window according to the national vaccination schedule in The Gambia (i.e., >1 day for HepB0 [37], >150 days for PENTA3, and >300 days for MCV1) [35]. We determined the age at vaccination (in days) for each vaccine by calculating the difference between vaccination dates and birth dates at the individual child level. Afterward, we aggregated the individual data from each survey cluster to generate observed cluster-level delayed HepB0, PENTA3 and MCV1 prevalence (Fig. 1a, b, and c).

2.4. Geospatial covariate data and selection

Geospatial covariates play a crucial role in geostatistical modelling by explaining and predicting the outcome variable(s) [38]. In our specific modelling approach, the inclusion of covariates aimed to improve the accuracy of outcome predictions, rather than serving an explanatory purpose to identify which covariates are driving the outcome [38]. We assembled a suite of socio-economic, environmental, and physical geospatial covariates from WorldPop which have been previously used in predictive modelling of vaccination coverage (Supplementary Table S1) [39]. These covariates were processed to generate 1 × 1-km^2 raster layers using ESRI ArcGIS v10.6. Subsequently, cluster-level data values were extracted from each standardised gridded layer using geographical coordinates from the 2019–20 GDHS, as previously described [20,22,23]. To accommodate DHS's confidentiality measures involving random cluster location displacement [40], we extracted mean covariate values from a 2 km and 5 km buffer around urban and rural clusters, respectively. We note that this covariate data extraction process can be further refined by using a population density layer to calculate weighted means within the buffers.

To determine the optimal set of covariates to be included for the predictive modelling of each outcome, we followed previous work by conducting a covariate selection process [21,23]. The selection process involved checking the relationship between the covariates and vaccination timeliness indicators and applying the log transformation where necessary to improve relationship; fitting single covariate models and ranking the covariates based on their predictive ability using predictive R^2 values; checking for multicollinearity and selecting between highly correlated covariates (correlation > 0.8 or variance inflation factor [VIF] > 4.0) using their ranks. Subsequently, the best model/combination of covariates for modelling the indicator was chosen using stepwise regression, with backward elimination based on Akaike Information Criterion (AIC) in a nonspatial framework using binomial regression models. For all the modelled indicators, we included urbanicity (i.e., urban or rural) as a covariate even if it was not chosen during the covariate selection process, as a way of accounting for the urban/rural stratification used in the survey design [41]. The covariates chosen for each vaccine are displayed as Supplementary Table S1 and Fig. S1.

To evaluate the need for accounting for spatial autocorrelation when modelling the indicators, we fitted binomial regression models with independent and identically distributed (iid) random effects, including the selected covariates for each indicator. Using the estimates of the iid random effect, we fitted a variogram in each case to assess the presence of residual spatial autocorrelation in the models (Supplementary Fig. S2). To enable the modelling of the prevalence of delayed vaccination at district level, we obtained relevant population estimates corresponding to the survey years for children one year and below in The Gambia from WorldPop [42]. The data were also used to generate the estimated population of infants affected with delayed HepB0, PENTA3 and MCV1 in all districts.

2.5. Geospatial modelling and validation

The general model we used to create 1x1-km^2 prevalence maps of

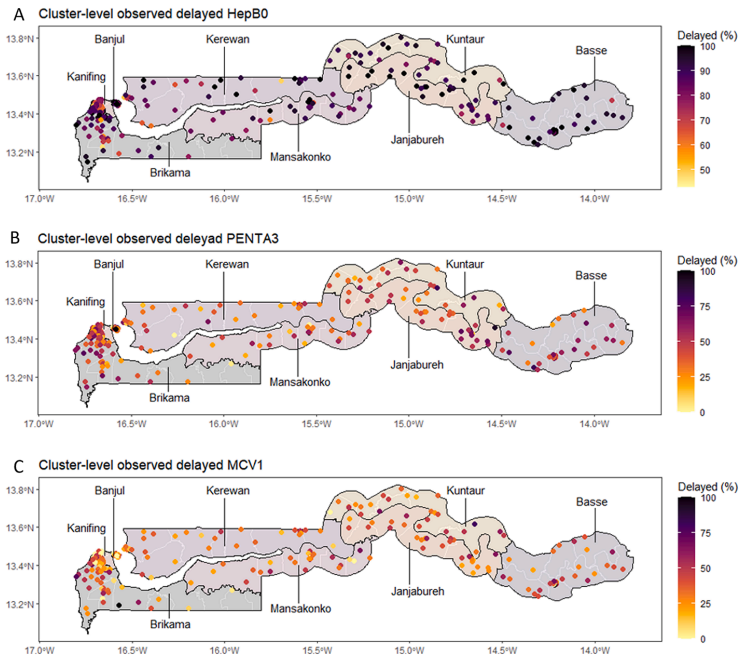


Fig. 1. Spatial distribution of the observed delayed HepB0, PENTA3, and MCV1 among children aged 12–35 months as recorded at the 2019–20 GDHS cluster level. Note. The cluster-level observed delayed vaccination was computed as the proportion of children sampled in a survey cluster who were vaccinated after the recommended national window, based on evidence from vaccination cards. *The names on the cluster-level observed maps indicate the eight Local Government Areas (LGAs) in The Gambia.*

delayed HepB0, PENTA3 and MCV1 is a fully Bayesian geostatistical technique with a binomial likelihood (see Supplementary material for details). The model was implemented using the integrated nested Laplace approximation—stochastic partial differential equation (INLA-SPDE) approach [43]. The INLA approach is a faster alternative to the traditional Markov chain Monte Carlo (MCMC) technique for performing approximate Bayesian inference. The approach uses numerical techniques to approximate the marginal posterior distributions of each of the unknown quantities in the model. The SPDE approach facilitates the estimation of the Gaussian spatial random effect by reducing the computational burden involved in the estimation of Σ_ω through a Gaussian Markov random field (GMRF) representation [43]. Further details on the implementation of the INLA-SPDE approach are provided in Utazi et al. [21,44].

To ensure consistency in the modelled prevalence (p) estimates for indicators of timeliness across each vaccine [i.e. p(early vaccination) + p (timely vaccination) + p(delayed vaccination) = 1 for each prediction location], we independently modelled p(timely vaccination) and p (delayed vaccination), and then derived p(early vaccination) as 1 - p (timely vaccination) - p(delayed vaccination) using the corresponding posterior samples. Where necessary, we adjusted the modelled estimates to ensure consistency across all indicators for each vaccine and prediction location. We chose to model p(timely vaccination) and p(delayed vaccination) because there were more observed cases of both events for the included vaccines compared to early vaccination, which increased the likelihood of obtaining more accurate estimates.

We summarised the calibrated draws for each predicted outcome as mean estimates and 95 % credible interval width (CIs). The predicted estimates at 1x1-km^2 were then aggregated to policy-relevant administrative areas (i.e., district- and ward-levels) as population-weighted means taken over all the grid cells falling within each areas in The Gambia by use of administrative boundaries from the Global Administrative Area (GADM) database [45]. We conducted a bivariate analyses and then created maps to visualize areas with a combination of high prevalence of delayed vaccination and a significant number of affected children.

In-sample model validation was done by comparing the model predictions at the first-administrative level (LGA) to the actual observed design-based direct survey estimates computed using the survey package (Supplementary Fig. S4) [46]. To evaluate the performance of our model on out-of-sample predictions, we used a 5-fold cross-validation approach. We quantified predictive performance using percentage bias, mean absolute error (MAE), and root mean squared error (RMSE). All of these metrics are described in the Supplementary Table S2. All analyses were performed using the R-INLA package in R (R Development Core Team, 2023) [47]. To ensure easy understanding of the main findings, the results section primarily presents cluster-level, 1x1-km^2 pixel, and district-level estimates (including uncertainty estimate) for each vaccine. Additional ward-level estimates (third-administrative level) are provided in the Supplementary material, but will be referenced throughout the results section.

3. Results

Table 1 below shows the design-based estimates of vaccination coverage and delayed vaccination at the national and LGA level in The Gambia. Overall, the vaccination coverage rates for all three vaccines was high, both at the national level and across all the eight LGAs (first-administrative level) in The Gambia. However, the prevalence of delayed vaccination is also high, particularly for HepB0.

3.1. Predicted delayed HepB0, PENTA3 and MCV1 vaccination at district and ward-level

The predicted prevalence of delayed HepB0 vaccination surpassed that of the other vaccines, indicating a higher degree of delay for this particular vaccine. At the 1 × 1-km^2 pixel-level, there were significant subnational disparities in the predicted prevalence of delayed vaccination throughout The Gambia. The highest pockets of predicted delayed vaccination were located in the central and eastern end of the country, while the coastal areas generally exhibited the lowest pockets of delays (Fig. 2a, b, and c). This pattern was consistent for all three vaccines studied, i.e., delayed HepB0, PENTA3, and MCV1 vaccinations.

The predicted prevalence of delayed HepB0 vaccination at the district level exhibited significant variation, ranging from 66.4 % to 95.0 %, representing a difference of over 25 % (Fig. 3a). Among the 49 districts in the country, 17 (34.7 %) had a HepB0 vaccination delay of ≥ 90 %, surpassing the national average. Notably, Basse LGA accounted for 41 % (7/17) of these districts, while Janjanbureh and Kuntaur LGAs each had 23.5 % (4/17) (Fig. 3a). A similar pattern emerged at the ward level, where the predicted prevalence of delayed HepB0 vaccination ranged from 63.5 % to 95.6 %. Janjanbureh, Kuntaur, and Basse LGAs, located

Table 1
Design-based Direct Survey Estimates of Vaccination Coverage and Delayed Vaccination Among 12–23 Months Old Children at the First-Administrative Level in The Gambia.

Administrative level	Coverage (95 % CI)			Delayed vaccination (95 % CI)*		
	HepB0	PENTA3	MCV1	HepB0	PENTA3	MCV1
National-level	98.9 (98.3, 99.5)	93.8 (92.2, 95.6)	90.6 (88.3, 92.8)	89.4 (81.9, 87.9)	42.8 (39.5, 46.1)	31.6 (28.5, 34.6)
Banjul	96.7 (93.4, 99.5)	90.1 (83.0, 97.1)	86.1 (77.1, 95.1)	89.1 (81.8, 96.4)	48.5 (34.3, 62.7)	26.9 (14.0, 39.9)
Basse	97.1 (95.3, 98.9)	92.3 (87.2, 97.4)	89.8 (85.2, 94.3)	95.9 (93.4, 98.4)	49.4 (43.5, 55.3)	39.6 (31.2, 48.1)
Brikama	98.5 (97.1, 99.9)	95.4 (92.8, 97.9)	89.6 (85.5, 93.7)	80.4 (74.4, 86.4)	42.4 (36.7, 48.7)	27.6 (22.5, 32.7)
Janjabureh	98.9 (97.5, 99.8)	92.5 (88.9, 96.1)	93.8 (90.3, 97.3)	95.3 (92.0, 98.7)	52.2 (44.9, 59.6)	40.6 (31.8, 49.4)
Kanifing	97.4 (95.0, 99.9)	86.7 (80.2, 93.2)	85.7 (78.1, 93.2)	80.8 (73.6, 87.9)	40.1 (31.5, 48.7)	30.3 (21.5, 39.1)
Kerewan	99.5 (98.7, 99.9)	98.7 (97.2, 99.8)	95.4 (92.2, 98.5)	84.2 (77.7, 90.7)	37.9 (30.7, 45.1)	30.7 (24.5, 36.8)
Kuntaur	98.0 (96.0, 99.7)	95.7 (92.8, 98.6)	94.4 (91.1, 97.7)	92.5 (88.4, 96.6)	44.8 (37.2, 52.5)	36.1 (28.9, 43.3)
Mansakonko	96.8 (94.1, 99.6)	97.0 (94.4, 99.6)	97.3 (94.4, 99.9)	88.0 (82.1, 93.9)	35.6 (26.4, 44.8)	34.8 (27.8, 41.8)

Note: The administrative levels mentioned in this table include the national level and the Local Government Area level (first administrative level). The direct-survey estimates from the 2019–20 The Gambia Demographic Survey are only representative at these specific levels, as well as at the urban and rural levels. *This indicates the prevalence of delayed vaccination among children who received vaccination and had documented dates of birth and vaccination. CI = Confidence Interval.

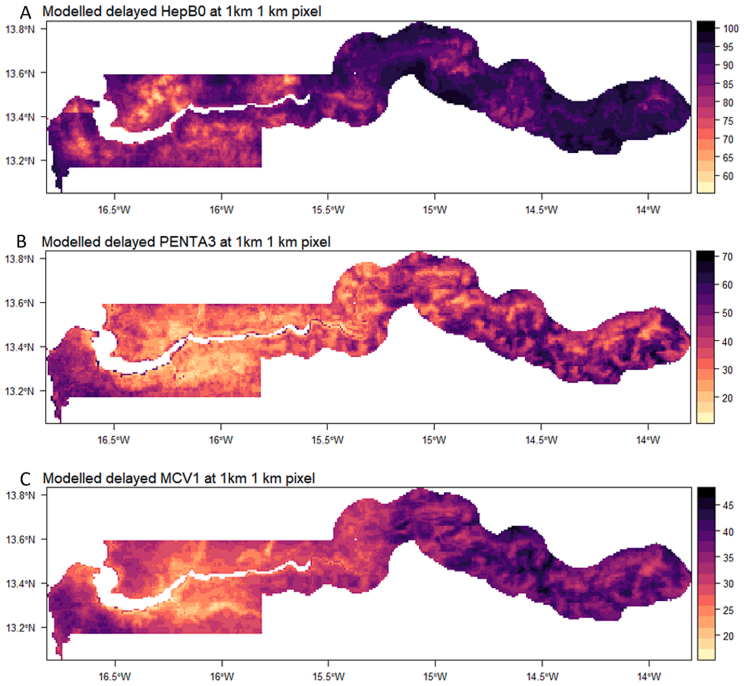


Fig. 2. (A) Predicted delayed birth-dose of hepatitis B vaccine (HepB0) at 1 × 1 km^2 pixel; (B) predicted delayed third-dose of pentavalent vaccine (PENTA3) at 1 × 1 km^2 pixel; (C) predicted delayed first-dose of the measles-containing vaccine (MCV1) at 1 × 1 km^2 pixel among 12–35 months children in The Gambia.

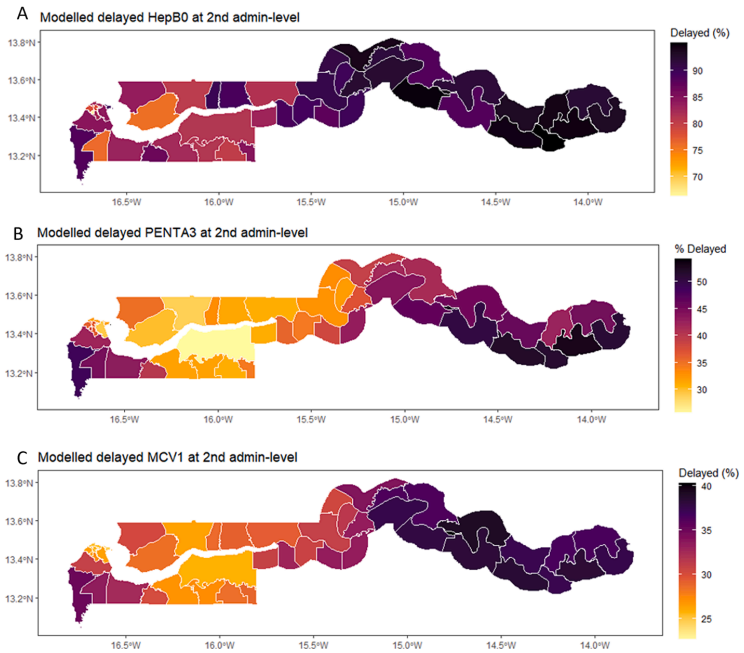


Fig. 3. (A) Predicted delayed birth-dose of hepatitis B vaccine (HepB0) at the district level; (B) predicted delayed third-dose of pentavalent vaccine (PENTA3) at the district level; (C) predicted delayed first-dose of the measles-containing vaccine (MCV1) at the district level among 12–35 months children in The Gambia.

in the central and eastern parts of the country had a higher concentration of wards with a delay of ≥ 90 % (Supplementary Fig. S5 and Table S3). It is worth noting that even in the coastal areas of Mansokonko, Banjul, Kerewan, and Kanifing LGAs, which generally had the lowest prevalence of delayed HepB0 vaccination, a few wards still experienced delays of ≥ 90 %.

The predicted prevalence of delayed PENTA3 vaccination at the district level ranged from 25.7 % to 54.1 %. Among the seven districts with a delay of 50 % or more in PENTA3 vaccination, four were located in Basse LGA, two in Janjanbureh LGA, and one in Banjul LGA (Fig. 3b). Similarly, at the ward level, the prevalence of delayed PENTA3 vaccination ranged from 24.2 % to 54.5 %. Basse LGA accounted for the majority (57 % or 8/14) of wards with a delay of 50 % or more (see Supplementary Fig. S6 and Table S4). The districts and wards with the lowest predicted prevalence of delayed PENTA3 vaccinations were primarily situated in coastal areas of The Gambia.

The predicted prevalence of delayed MCV1 vaccination at the district level ranged from 22.7 % to 40.2 %, as shown in Fig. 3c. Of the top 10 districts with delayed MCV1 vaccinations (i.e., delay of 37 % or more), five (50 %) were located in Basse LGA in the eastern part of The Gambia, while four (40 %) were in Janjanbureh LGA, and one (10 %) was in Kuntaur LGA in central parts (Fig. 3c and Supplementary Table S5). Similarly, the top 10 wards with the highest delayed MCV1 vaccinations (i.e., delay of 38 % or more) were also located in Basse, Janjanbureh, and Kuntaur LGAs (Supplementary Table S7).

Fig. 4 presents the summary of the pattern of delayed vaccination, categorized as tertiles, for all vaccines in all the wards in The Gambia. In the Basse LGA, all the districts, except one, fell within the highest tertile of delayed vaccination for the three vaccines.

The 95 % credible interval width around the modelled estimates, which reflects the uncertainty in the estimates, was generally narrow (i.e., <15 %) for the three vaccines and outcomes examined (Fig. 4a, b, and c). This indicates that the modelled estimates are relatively robust and precise. However, it is worth noting that the uncertainty was generally highest for districts and wards located in Brikama LGA, which is situated in the coastal area of the country (Fig. 5).

3.2. Districts with a combination of high estimated prevalence and a significant population of affected infants

Overall, there was some similarity in the spatial pattern of districts where there was a combination of high estimated prevalence and a significant population of affected infants by delayed HepB0, PENTA3 and MCV1 (Fig. 5). Our findings revealed that certain districts in Basse and Janjabureh LGAs in the eastern and central Gambia, as well as in Brikama LGA in coastal Gambia, had a spatial overlap of high estimated prevalence and a significant population of affected infants (Fig. 6 and Supplementary Table S6). In particular, there was a consistent spatial overlap of high delayed vaccination and a significant number of affected children across four districts in Basse LGA. These districts include Kantora, Jimara, Basse, and Tumana, and this pattern was observed for all the vaccines studied.

4. Discussion

The routine childhood vaccination program in The Gambia has achieved remarkable success, maintaining vaccination coverage of at least 90 % for most childhood vaccines for over a decade [18,48]. This accomplishment has positioned the country as a model for vaccine delivery in many sub-Saharan African countries. However, our findings emphasize an important point: relying solely on overall vaccination coverage estimates may not accurately measure immunisation program quality. Significantly, our results offer valuable insights into the performance of the vaccine delivery system in The Gambia applying novel methodology that could be used in other countries.

Previous studies on vaccination timeliness in The Gambia did not incorporate spatial analysis [49–51], thus, missing the opportunity to identify specific areas or "hotspots" of delayed childhood vaccinations. The estimates from these studies serve as an important initial step in exploring vaccination timeliness, but they are insufficient for targeted

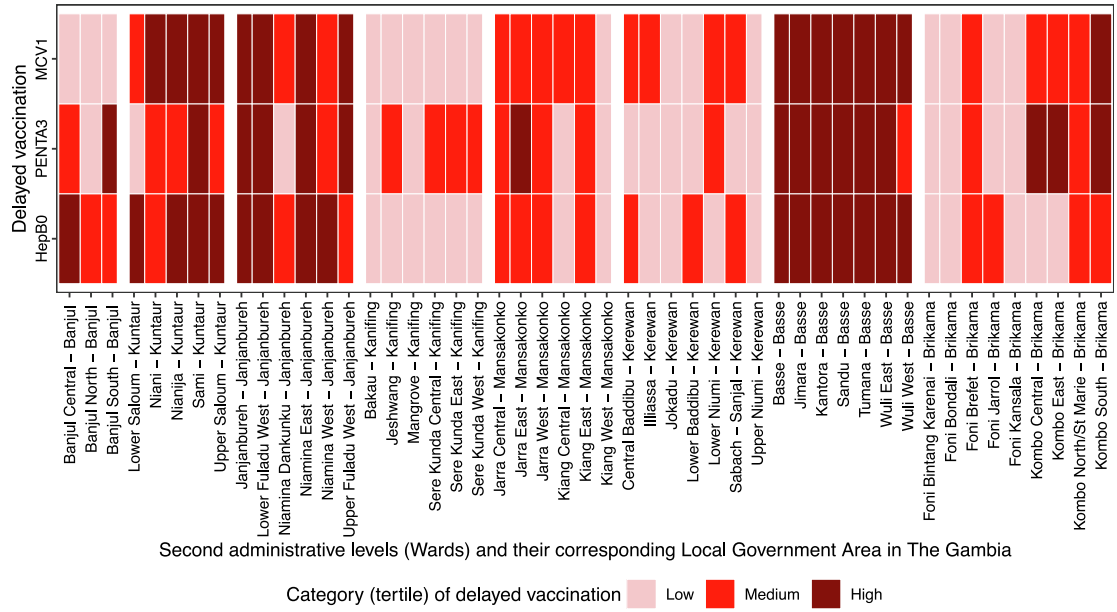


Fig. 4. The summary of the pattern of modelled estimates for delayed vaccination, categorized as tertiles, for the three vaccines (HepB0, PENTA3 and MCV1) in all the 49 districts in The Gambia. Note. Each district (second administrative level) is shown with their corresponding LGA (first administrative level).

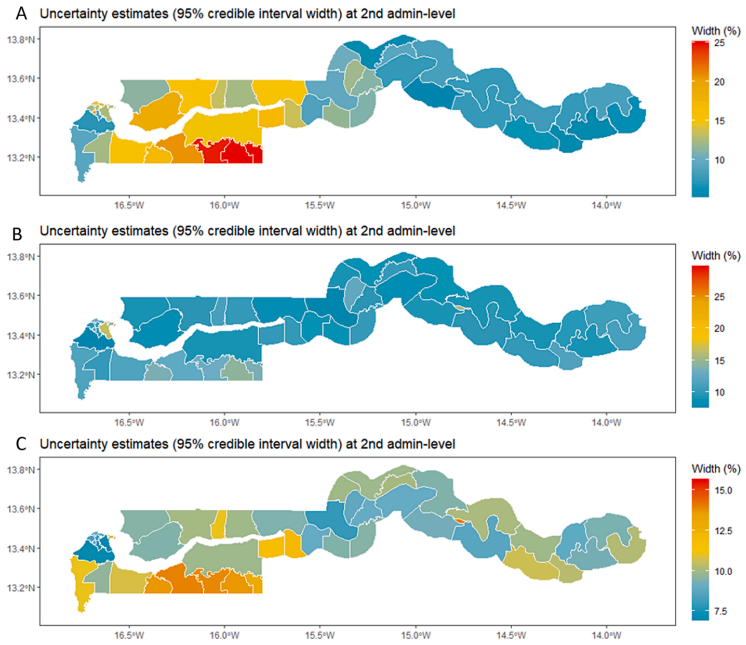


Fig. 5. (A) Uncertainty estimate (95 % credible interval width) around predicted delayed HepB0 at district level in The Gambia; (B) uncertainty estimate (95 % credible interval width) around predicted delayed PENTA3 at district level in The Gambia; (C) uncertainty estimate (95 % credible interval width) around predicted delayed MCV1 at district level among 12–35 months children in The Gambia.

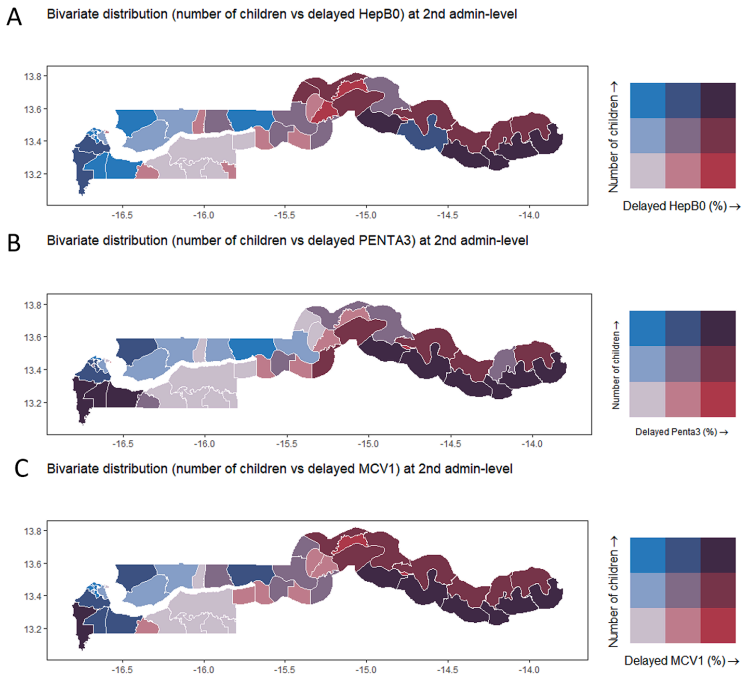


Fig. 6. Bivariate maps showing the spatial relationship between delayed HepB0 (A), PENTA3 (B), MCV1 (C) and the number of affected children across the 49 districts (second administrative level) in The Gambia.

programmatic interventions because they did not identify pockets of vulnerabilities that could benefit from targeted interventions. Our analysis is the first of its kind to provide a country-wide, high-resolution spatial estimation of the timeliness of routine childhood vaccination within the context of an LMIC. Our data reveal significant subnational inequalities in delayed HepB0, PENTA3, and MCV1 vaccinations, primarily concentrated in The Gambia's central and eastern regions which are also the most economically disadvantaged regions [52]. Conversely, children in western coastal areas experienced less vaccination delay, further corroborating findings from a previous large cross-sectional study conducted in The Gambia [51]. National-level estimates of vaccination timeliness mask these subnational pockets of delayed vaccination, thereby potentially exposing children in those areas to the risk of measles and pertussis outbreaks or vertical transmission of hepatitis B virus.

Family sociodemographic barriers, health facility readiness, and physical accessibility of vaccination services, among other factors, have previously been reported to impact vaccine delivery and uptake [53,54], and they may help explain the observed pattern of subnational inequalities in our study. Previous research has established a clear connection between geographical isolation from service delivery channels and the coverage of routine childhood vaccines [55,56]. However, the extent to which these factors affect vaccination timeliness remains largely unexplored. To achieve optimal vaccination coverage, The Gambia currently employs a unique system that combines fixed facilities and outreach sites. Most fixed health facilities are located in coastal areas and provide services at least once a week [57]. Outreach sites, on the other hand, serve remote locations, potentially more prevalent in the eastern region of The Gambia, at least once a month [57]. Travel difficulties between households, fixed facilities and outreach sites may hinder travel and result in delayed uptake and delivery of vaccines to remote communities. This two-tier routine vaccine delivery mechanism may partially explain the spatial pattern of delayed vaccination observed in our study. However, exploring other potential health system or structural drivers contributing to the significant subnational inequalities reported in our data is a crucial next step.

While the majority of districts or wards with the highest prevalence of delays were not located in the coastal areas of The Gambia, we observed that some districts had a combination of high prevalence and a significant absolute number of children with delayed vaccinations in this area. This finding is unsurprising, as it reflects a higher population density in these areas. More children likely live in districts and wards in the country's more urban and coastal regions. These findings demonstrate the usefulness of geospatial analysis in uncovering areas with co-occurrence of high under-vaccination (including delays) and a significant absolute number of children. Clusters or pockets of locations with high population density, under- or delayed vaccination can sustain outbreaks of VPDs such as measles and pertussis. Previous studies have demonstrated the significant impact of clustering or pockets of under-vaccinated subpopulations on the occurrence of disease outbreaks, particularly in countries that have already achieved high overall coverage rates [58,59]. While we have not established a direct link between vaccination timeliness and VPDs outbreaks, improving timeliness potentially plays a role in preventing outbreaks or contributing to achieving disease elimination in the context of high coverage.

Our findings provide valuable insights for immunization program managers and decision-makers, offering a tool to visualize and comprehend local patterns of vaccination timeliness more precisely. This information can play a crucial role in identifying districts where routine vaccine delivery systems require strengthening and prioritizing interventions for maximum impact. It is especially significant considering our data demonstrated that four districts in Basse consistently exhibited high delayed vaccination and a significant number of affected children across all the vaccines studied. This finding suggests that these districts may have peculiar health system or other issues that could benefit from targeted interventions. Our findings underscore the significance of employing fine-scale spatial mapping techniques to investigate timeliness, particularly in countries like The Gambia, where overall vaccination coverage is high. This approach is crucial as it can reveal untimely vaccination patterns at lower administrative levels that may be masked by the aggregated data at higher levels.

In future work, we need to explore the spatiotemporal pattern of untimely vaccination to determine whether the subnational heterogeneities in delayed vaccination identified in our study persist over time or exhibit seasonal or monthly variations. Such analysis could benefit from geocoded longitudinal population survey data. One strength of using such data is the ability to link vaccination data with other epidemiological and disease surveillance data, and the fact that they cover under-documented or often missed communities. There is also a need to investigate whether there is a spatial relationship between areas that report measles outbreaks, low overall MCV1 coverage rates, and high prevalence of delayed MCV1. This can be done by using longitudinal vaccination data linked to measles epidemiological or disease-surveillance data. When triangulated with other datasets to produce additional metrics, such data could potentially shed more light on the impact of untimely vaccination on population immunity and enable the programmatic assessment of EPI performance. In future work, we will also consider developing a methodology for mapping indicators of timeliness of routine childhood vaccination using a combination of geolocated survey data and District Health Information Software (i.e., DHIS2) data. In a multi-temporal analysis, this could have the added benefit of improving the accuracy of the modelled estimates.

Our study provides valuable insights into subnational patterns of vaccine timeliness using a probabilistic spatial modelling framework. However, the dataset analyzed and the methods deployed are subject to some limitations. First, the sampling frames used in the 2019–20 GDHS may have missed hard-to-reach or disadvantaged populations. This could lead to an under- or over-estimation of the prevalence of delayed vaccination in certain areas. To address this, we recommend using more accurate geocoded data from targeted surveys in future analyses to obtain better estimates in such locations. Second, to ensure confidentiality of respondents, the GDHS randomly displaced the geographical coordinates at the cluster level. This displacement is restricted so that the points remain within the country and within the DHS survey region. While we created buffers around the coordinates in rural and urban locations in line with previous approaches [20,22,23], there might have been some residual influence on the modelled estimates, especially at a more granular level. Thirdly, excluding children without HBR may lead to potential under- or overestimation of the timeliness estimates, especially if there is differential availability of records across clusters, districts or wards. Nevertheless, it is worth noting that HBR and vaccination records availability was high (~93 %) in the 2019–20 GDHS, which likely limited such potential bias in our analysis. Lastly, it is important to acknowledge that the 2019–20 GDHS sample was designed to be representative at the national and regional levels, considering urban/rural stratification, and not at the district or ward level. However, the Bayesian spatial modelling approach utilized in this analysis has been well validated and is known to provide robust estimates. Despite these limitations, our analysis provides an important first step in refining interventions to strengthen vaccination programs in a targeted and cost-effective manner. This is especially important in the wake of the COVID-19 pandemic, as we need to ensure that children receive their routine vaccines in a timely manner so they are protected from VPDs. Our findings can also be used to assess the progress made in expanding immunisation and ensuring effective protection for children following the implementation of such interventions.

5. Conclusion

This study identified all districts and wards in The Gambia where there was a combination of a high estimated prevalence of delayed vaccination and a significant population of affected infants. Our

methodological approach enabled us to identify districts and wards with the highest prevalence of delayed vaccination, which would not have been possible using large area estimates. This information is valuable for immunisation programme managers as it allows them to identify the most vulnerable districts that could benefit from targeted immunisation interventions. Our results and existing subnational-level estimates of vaccination coverage provide a more detailed understanding of the overall quality of routine childhood vaccination in The Gambia. This information is valuable for identifying areas that require targeted interventions to improve vaccination timeliness. Additionally, our approach can be applied to other countries, serving as a model to guide immunisation programs and service providers that seek to enhance the overall quality of the immunisation system.

Funding

This project is part of the EDCTP2 Programme supported by the European and Developing Countries Clinical Trials Partnership (grant number TMA2019CDF-2734 – TIMELY). OW was also supported by an Imperial College London Wellcome Trust Institutional Strategic Support Fund (ISSF) (grant no RSRO_P67869). KM is supported by joint Centre funding from the UK Medical Research Council and Department for International Development [MR/R0156600/1]. CEU is supported by funding from the Bill & Melinda Gates Foundation (Investment ID INV-003287). The Vaccines and Immunity Theme (OW, UO, and BK) is jointly funded by the UK MRC and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 Programme supported by the EU (MC UP_A900/1122, MC UP A900/115). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

Oghenebrume Wariri: Conceptualization, Methodology, Resources, Project administration, Data curation, Writing – original draft. **Chigozie Edson Utazi:** Conceptualization, Methodology, Resources, Supervision, Data curation, Writing – review & editing. **Uduak Okomo:** Conceptualization, Methodology, Supervision, Writing – review & editing. **C. Jessica E. Metcalf:** Conceptualization, Methodology, Writing – review & editing. **Malick Sogur:** Conceptualization, Methodology, Writing – review & editing. **Sidat Fofana:** Conceptualization, Methodology, Writing – review & editing. **Kris A. Murray:** Conceptualization, Methodology, Resources, Writing – review & editing. **Chris Grundy:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Beate Kampmann:** Conceptualization, Resources, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The 2019–20 GDHS survey data used for this study is publicly available and can be downloaded from the websites of the DHS program after securing approval.

All the R codes developed for the purposes of this analysis are freely available in open repository at: https://github.com/drwariri/Mapping-the-timeliness-of-routine-childhood-vaccination-in-The-Gambia-a-spatial-modelling-study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.08.004.

References

[1] United Nations Children's Fund. Immunization road map: 2018-2030. New York: UNICEF; 2018.
[2] Ozawa S, Clark S, Portnoy A, Grewal S, Brenzel L, Walker DG. Return on investment from childhood immunization in low-and middle-income countries, 2011–20. Health Aff 2016;35(2):199–207.
[3] World Health Organization. Immunization Agenda 2030 - a global strategy to leave no one behind. Geneva; 2021.
[4] Li X, Mukandavire C, Cucunubá ZM, Echeverria Londono S, Abbas K, Clapham HE, et al. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Lancet 2021;397(10272):398–408.
[5] World Health Organization. COVID-19 pandemic fuels largest continued backslide in vaccinations in three decades; 2023. https://www.who.int/news/item/15-07-2022-covid-19-pandemic-fuels-largest-continued-backslide-in-vaccinations-in-three-decades (accessed 23 March 2023).
[6] World Health Organization. Harmonizing vaccination coverage measures in household surveys: A primer. Geneva, Switzerland: WHO; 2019.
[7] World Health Organization. Training for mid-level managers (MLM) module 5: monitoring the immunization system. Geneva; 2008.
[8] Walton S, Cortina-Borja M, Dezateux C, Griffiths LJ, Tingay K, Akbari A, et al. Measuring the timeliness of childhood vaccinations: Using cohort data and routine health records to evaluate quality of immunisation services. Vaccine 2017;35(51):7166–73.
[9] Galles NC, Liu PY, Updike RL, Fullman N, Nguyen J, Rolfe S, et al. Measuring routine childhood vaccination coverage in 204 countries and territories, 1980–2019: a systematic analysis for the Global Burden of Disease Study 2020, Release 1. Lancet 2021;398(10299):503–21.
[10] Plotkin SA. Vaccines: Past, present and future. Nat Med 2005;11(S4):S5–11.
[11] MacDonald SE, Russell ML, Liu XC, Simmonds KA, Lorenzetti DL, Sharpe H, et al. Are we speaking the same language? An argument for the consistent use of terminology and definitions for childhood vaccination indicators. Hum Vaccin Immunother 2019;15(3):740–7.
[12] Nic Lochlainn LM, de Gier B, van der Maas N, van Binnendijk R, Strebel PM, Goodman T, et al. Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis. Lancet Infect Dis 2019;19(11):1246–54.
[13] Borràs E, Urbiztondo L, Costa J, Batalla J, Torner N, Plasencia A, et al. Measles antibodies and response to vaccination in children aged less than 14 months: implications for age of vaccination. Epidemiol Infect 2012;140(9):1599–606.
[14] Guerra FA. Delays in immunization have potentially serious health consequences. Paediatr Drugs 2007;9(3):143–8.
[15] Hübschen JM, Gouandjika-Vasilache I, Dina J. Measles. Lancet 2022;399(10325):678–90.
[16] Henderson DA, Dunston FJ, Fedson DS, et al. The measles epidemic: the problems, barriers, and recommendations. JAMA 1991;266(11):1547–52.
[17] Wariri O, Edem B, Nkereuwem E, Nkereuwem OO, Umeh G, Clark Ed, et al. Tracking coverage, dropout and multidimensional equity gaps in immunisation systems in West Africa, 2000–2017. BMJ Glob Health 2019;4(5):e001713.
[18] Wariri O, Nkereuwem E, Erondu NA, et al. A scorecard of progress towards measles elimination in 15 west African countries, 2001-19: a retrospective, multicountry analysis of national immunisation coverage and surveillance data. Lancet Glob Health 2021;9(3):e280–90. https://doi.org/10.1016/S2214-109X(20)30481-2.
[19] Masters NB, Eisenberg MC, Delamater PL, Kay M, Boulton ML, Zelner J. Fine-scale spatial clustering of measles nonvaccination that increases outbreak potential is obscured by aggregated reporting data. Proc Natl Acad Sci 2020;117(45):28506–14.
[20] Mosser JF, Gagne-Maynard W, Rao PC, Osgood-Zimmerman A, Fullman N, Graetz N, et al. Mapping diphtheria-pertussis-tetanus vaccine coverage in Africa, 2000–2016: a spatial and temporal modelling study. Lancet 2019;393(10183):1843–55.
[21] Utazi CE, Aheto JMK, Wigley A, Tejedor-Garavito N, Bonnie A, Nnanatu CC, et al. Mapping the distribution of zero-dose children to assess the performance of vaccine delivery strategies and their relationships with measles incidence in Nigeria. Vaccine 2023;41(1):170–81.
[22] Utazi CE, Thorley J, Alegana VA, Ferrari MJ, Takahashi S, Metcalf CJE, et al. Mapping vaccination coverage to explore the effects of delivery mechanisms and inform vaccination strategies. Nat Commun 2019;10(1):1633.
[23] Utazi CE, Thorley J, Alegana VA, Ferrari MJ, Takahashi S, Metcalf CJE, et al. High resolution age-structured mapping of childhood vaccination coverage in low and middle income countries. Vaccine 2018;36(12):1583–91.
[24] Local Burden of Disease Vaccine Coverage Collaborators. Mapping routine measles vaccination in low- and middle-income countries. Nature 2021;589(7842):415–9.
[25] Masters NB, Wagner AL, Boulton ML. Vaccination timeliness and delay in low- and middle-income countries: a systematic review of the literature, 2007–2017. Hum Vaccin Immunother 2019;15(12):2790–805.
[26] Wariri O, Okomo U, Kwarshak YK, Utazi CE, Murray K, Grundy C, et al. Timeliness of routine childhood vaccination in 103 low-and middle-income countries,

1978–2021: A scoping review to map measurement and methodological gaps. PLOS Global Public Health 2022;2(7):e0000325.
[27] Gavi; UNICEF; HealthEnabled. Leveraging geospatial technologies and data to strengthen immunisation programmes: rapid guidance for investment planning; 2021.
[28] Wariri O, Utazi CE, Okomo U, Sogur M, Murray KA, Grundy C, et al. Timeliness of routine childhood vaccination among 12–35 months old children in The Gambia: Analysis of national immunisation survey data, 2019-2020. PLoS One 2023;18(7):e0288741.
[29] Wilson P, Taylor G, Knowles J, Blyth E, Laux J, Lohr J, et al. Missed hepatitis B birth dose vaccine is a risk factor for incomplete vaccination at 18 and 24 months. J Infect 2019;78(2):134–9.
[30] Oster NV, Williams EC, Unger JM, et al. Hepatitis B birth dose: first shot at timely early childhood vaccination. Am J Prev Med 2019; 57(4): e117–e24.
[31] McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep Recomm Rep 2013;62(4):1–34.
[32] World Health Organization. Surveillance for Vaccine Preventable Diseases (VPDs); 2022. https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance/surveillance-for-vpds (accessed 19 July 2022).
[33] Worldometer. The Gambia Population; 2021. https://www.worldometers.info/world-population/gambia-population/ (accessed November 19 2021).
[34] World Health Organization. History of the measles vaccine; 2023. https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-measles-vaccination (accessed 22 April 2023).
[35] World Health Organization. Vaccination schedule for Gambia; 2023. https://immunizationdata.who.int/pages/schedule-by-country/gmb.html?DISEASECODE=&TARGETPOP_GENERAL= (accessed 29 January 2023).
[36] Gambia Bureau of Statistics (GBoS) and ICF. The Gambia Demographic and Health Survey 2019-20. Banjul, The Gambia and Rockville, Maryland, USA; 2021.
[37] World Health Organization. Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination. Geneva, Switzerland: World Health Organization; 2015.
[38] Giorgi E, Fronterrè C, Macharia PM, Alegana VA, Snow RW, Diggle PJ. Model building and assessment of the impact of covariates for disease prevalence mapping in low-resource settings: to explain and to predict. J R Soc Interface 2021;18(179):20210104.
[39] WorldPop. Geospatial covariate data layers; 2023. https://hub.worldpop.org/project/categories?id=14 (accessed 16 January 2023).
[40] Mayala B, Fish TD, Eitelberg D, Dontamsetti T. The DHS Program Geospatial Covariate Datasets Manual (Second Edition). Rockville, Maryland, USA: ICF; 2018.
[41] Dong TQ, Wakefield J. Modeling and presentation of vaccination coverage estimates using data from household surveys. Vaccine 2021;39(18):2584–94.
[42] Tatem AJ. WorldPop, open data for spatial demography. Sci Data 2017;4(1):170004.
[43] Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. J Roy Statist Soc: Series b (Statist Methodol) 2009; 71(2): 319–92.
[44] Utazi CE, Wagai J, Pannell O, Cutts FT, Rhoda DA, Ferrari MJ, et al. Geospatial variation in measles vaccine coverage through routine and campaign strategies in Nigeria: Analysis of recent household surveys. Vaccine 2020;38(14):3062–71.
[45] Runfola D, Anderson A, Baier H, Crittenden M, Dowker E, Fuhrig S, et al. geoBoundaries: A global database of political administrative boundaries. PLoS One 2020;15(4):e0231866.
[46] Lumley T. Analysis of complex survey samples. J Stat Softw 2004;9(8):1–19.
[47] Lindgren F, Rue H. Bayesian spatial modelling with R-INLA. J Stat Softw 2015;63:1–25.
[48] Wariri O, Edem B, Nkereuwem E, Nkereuwem OO, Umeh G, Clark Ed, et al. Tracking coverage, dropout and multidimensional equity gaps in immunisation systems in West Africa, 2000–2017. BMJ Global Health 2019;4(5):e001713.
[49] Odutola A, Afolabi MO, Ogundare EO, Lowe-Jallow YN, Worwui A, Okebe J, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. BMC Health Serv Res 2015;15(1).
[50] Miyahara R, Jasseh M, Gomez P, Shimakawa Y, Greenwood B, Keita K, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. *Vaccine* 2016;34(29):3335–41.
[51] Scott S, Odutola A, Mackenzie G, et al. Coverage and timing of children's vaccination: an evaluation of the expanded programme on immunisation in The Gambia. PloS one 2014; 9(9): e107280.
[52] Gambia Bureau of Statistics (GBoS). Integrated Household Survey 2015/16. Volume II: Socio-economic Characteristics. Banjul: Gambia Bureau of Statistics; 2017.
[53] Galadima AN, Zulkefli NAM, Said SM, Ahmad N. Factors influencing childhood immunisation uptake in Africa: a systematic review. BMC Public Health 2021;21(1):1475.
[54] Phillips DE, Dieleman JL, Lim SS, Shearer J. Determinants of effective vaccine coverage in low and middle-income countries: a systematic review and interpretive synthesis. BMC Health Serv Res 2017;17(1):681.
[55] Metcalf CJE, Tatem A, Bjornstad ON, Lessler J, O'reilly K, Takahashi S, et al. Transport networks and inequities in vaccination: remoteness shapes measles vaccine coverage and prospects for elimination across Africa. Epidemiol Infect 2015;143(7):1457–66.
[56] Blanford JI, Kumar S, Luo W, MacEachren AM. It's a long, long walk: accessibility to hospitals, maternity and integrated health centers in Niger. Int J Health Geogr 2012;11(1):24.
[57] Ministry of Health The Gambia. Draft policy of the expanded programme on immunisation, Republic of The Gambia. Banjul, The Gambia: Ministry of Health The Gambia; 2006.
[58] Truelove SA, Graham M, Moss WJ, Metcalf CJE, Ferrari MJ, Lessler J. Characterizing the impact of spatial clustering of susceptibility for measles elimination. Vaccine 2019;37(5):732–41.
[59] Sanyaolu A, Okorie C, Marinkovic A, et al. Measles Outbreak in Unvaccinated and Partially Vaccinated Children and Adults in the United States and Canada (2018-2019): A Narrative Review of Cases. Inquiry 2019; 56: 46958019894098.

Chapter 5: The impact of the COVID-19 pandemic on the timeliness and coverage of routine childhood vaccination in the Gambia (Research Paper)

5.1 Overview of Chapter

This chapter addresses the third objective of my PhD which was; "*To determine the impact of the COVID-19 pandemic on the timeliness and coverage of routine childhood vaccination in the Gambia*".

This chapter tests the following hypotheses:

- *The COVID-19 pandemic will result in a significant increase in the proportion of untimely childhood vaccinations, including both early and delayed vaccinations, as well as a decrease in routine childhood vaccination coverage in The Gambia, particularly during the peaks of epidemiological waves*.

The research paper addressing the objective in this chapter was published in BMJ Global Health, with the following full bibliographic information:

Wariri O, Utazi CE, Okomo U, Sowe A, Sogur M, Fofanna S, Ezeani E, Saidy L, Sarwar G, Dondeh BL, Murray KA, Grundy C, Kampmann B. (2023) Impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in the Gambia, 2015–2021. BMJ Global Health.

The supplementary material, accompanying the research paper in this chapter is included as **Appendix 9**.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1509291	**Title**	DR
First Name(s)	Oghenebrume		
Surname/Family Name	Wariri		
Thesis Title	Timeliness of routine childhood vaccination in The Gambia: examining the burden, spatial pattern, determinants and the impact of COVID-19 pandemic		
Primary Supervisor	Chris Grundy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Global Health		
When was the work published?	December 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?
Please list the paper's authors in the intended authorship order:

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised this study and led it's execution. I cleaned the data, merged datasets, undertook all the analysis, and interpreted the results. I wrote the initial manuscript draft and handled all referencing. I handled the submission, the reviewer responses, and the re-submisison process.

SECTION E

Student Signature	[redacted]
Date	20th February 2024

Supervisor Signature	Chris Grundy
Date	21 Feb 2024

Original research

BMJ Global Health

Impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in the Gambia, 2015–2021

Oghenebrume Wariri ,[1,2,3] Chigozie Edson Utazi ,[4,5] Uduak Okomo,[1,6] Alieu Sowe,[7] Malick Sogur,[7] Sidat Fofanna,[7] Esu Ezeani,[8] Lamin Saidy,[9] Golam Sarwar,[8] Bai-Lamin Dondeh,[9] Kris A Murray,[10] Chris Grundy,[2] Beate Kampmann[1,3,11]

To cite: Wariri O, Utazi CE, Okomo U, *et al*. Impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in the Gambia, 2015–2021. *BMJ Glob Health* 2023;**8**:e014225. doi:10.1136/bmjgh-2023-014225

Handling editor Seye Abimbola

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2023-014225).

KAM, CG and BK are joint senior authors.

Received 11 October 2023
Accepted 10 December 2023

For numbered affiliations see end of article.

Correspondence to
Dr Oghenebrume Wariri; oghenebrume.wariri@lshtm.ac.uk

ABSTRACT

Introduction The COVID-19 pandemic caused widespread morbidity and mortality and resulted in the biggest setback in routine vaccinations in three decades. Data on the impact of the pandemic on immunisation in Africa are limited, in part, due to low-quality routine or administrative data. This study examined coverage and timeliness of routine childhood immunisation during the pandemic in The Gambia, a country with an immunisation system considered robust.

Methods We obtained prospective birth cohort data of 57 286 children in over 300 communities in two health and demographic surveillance system sites, including data from the pre-pandemic period (January 2015–February 2020) and the three waves of the pandemic period (March 2020–December 2021). We determined monthly coverage and timeliness (early and delayed) of the birth dose of hepatitis B vaccine (HepB0) and the first dose of pentavalent vaccine (Penta1) during the different waves of the pandemic relative to the pre-pandemic period. We implemented a binomial interrupted time-series regression model.

Result We observed no significant change in the coverage of HepB0 and Penta1 vaccinations from the pre-pandemic period up until the periods before the peaks of the first and second waves of the pandemic in 2020. However, there was an increase in HepB0 coverage before as well as after the peak of the third wave in 2021 compared with the pre-pandemic period (pre-third wave peak OR = 1.83, 95% CI 1.06 to 3.14; post-third wave period OR=2.20, 95% CI 1.23 to 3.92). There was some evidence that vaccination timeliness changed during specific periods of the pandemic. Early Penta1 vaccination decreased by 70% (OR=0.30, 95% CI 0.12 to 0.78) in the period before the second wave, and delayed HepB0 vaccination decreased by 47% (OR=0.53, 95% CI 0.29 to 0.97) after the peak of the third wave in 2021.

Conclusion Despite the challenges of the COVID-19 pandemic, The Gambia's routine vaccination programme has defied the setbacks witnessed in other settings and remained resilient, with coverage increasing and timeliness improving during the second and third waves. These findings highlight the importance of having adequate surveillance systems to monitor the impact of large shocks to vaccination coverage and timeliness.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several studies conducted in North America, Europe and Asia showed that the coverage of routine immunisation declined, especially in the early phase of the COVID-19 pandemic.

⇒ While mortality and morbidity from the pandemic were comparatively lower in Africa, data on the impact of the pandemic on routine vaccination are limited, partly due to low-quality routine or administrative data.

WHAT THIS STUDY ADDS

⇒ We used monthly prospective birth cohort data from over 300 communities in 2 large health and demographic surveillance systems in The Gambia, covering 5 years before and 2 years into the COVID-19 pandemic, to explore 2 important dimensions of immunisation system performance: coverage and timeliness.

⇒ Our findings suggest that the COVID-19 pandemic did not have a significant negative impact on routine vaccination in The Gambia.

⇒ Rather, we observed that coverage and timeliness of vaccinations remained stable in the first year of the pandemic, with significant improvement in both metrics in the second year compared with the pre-pandemic period.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that Gambia's routine immunisation system was resilient and absorbed the additional shocks imposed by the pandemic.

⇒ Thus, it can be a model for other countries to learn from and adapt strategies to their context in future public health emergencies.

INTRODUCTION

Public health emergencies, such as natural disasters, humanitarian crises, armed conflicts and major disease outbreaks resulting in epidemics and pandemics, can strain country-level health systems and lead to a decline in the provision, demand and utilisation of basic health services.[1–3] This can worsen the burden of infectious diseases and contribute to increased mortality. For example, during the Ebola outbreak in West Africa from 2014 to 2015, there was a significant reduction in healthcare utilisation, including routine immunisation, especially in regions with a high incidence of Ebola cases.[4 5] In Liberia and Guinea, the number of children receiving measles vaccinations dropped by 30% and 33%, respectively, following the Ebola outbreak in 2014. This decline was followed by further drops of 25% and 26% in 2015.[5] The decline in routine immunisation coverage led to an increase in the number of children susceptible to measles and a surge in measles cases that persisted for 2 years following the Ebola outbreak.[5] The COVID-19 pandemic, which began in December 2019 and caused morbidity and mortality in nearly all countries, also resulted in the biggest setback in routine vaccinations in three decades. In the second year of the pandemic, 18.2 million children globally did not receive the first dose of the diphtheria-tetanus-pertussis containing vaccine, and an additional 6.8 million children were undervaccinated.[6] These examples show that even a temporary interruption of basic health services, such as routine immunisation, during public health emergencies can lead to secondary health crises. This underscores the importance of monitoring the impact of COVID-19 on routine immunisation. Monitoring can help to identify potentially significant adverse changes and inform the planning of mitigating measures for future similar circumstances.

In addition to the direct effects of the pandemic, such as morbidity and mortality caused by the virus, there are well-documented indirect effects on services like routine immunisation, especially in the initial phase of the COVID-19 pandemic. Such effects have been extensively documented, especially in relation to services such as routine immunisation.[7–12] They stem from a combination of factors, including the negative impact of the physical measures implemented to reduce COVID-19 infection, such as lockdowns, movement restrictions and the suspension of elective and preventive visits to healthcare facilities. Furthermore, even when medical services are available, people were unable to access them due to transport interruptions, economic hardship and fear of COVID-19 exposure. Healthcare workers may experience similar challenges and concerns, as was evident in the early pandemic phase when access to personal protective equipment was unreliable in many contexts.[13] These effects are thought to be higher in low-income and middle-income countries with limited healthcare resources and fragile health systems.[7] Recognising the detrimental effects on routine immunisation services, the WHO promptly issued guidance for sustaining routine immunisation activities as early as March 2020.[14–16] These guidance strongly recommended that, to the extent feasible and in alignment with local contexts and COVID-19 responses, routine immunisation activities for all eligible individuals should maintain their status as a priority.

Studies examining the impact of the pandemic on routine childhood immunisation gained momentum as early as the first year of the pandemic. A global WHO survey, early in 2020, reported a 70% disruption to routine immunisation services, indicating that services were affected in most countries.[17] Several studies have been conducted at country level in North America,[8 18 19] Europe[11 20] and Asia.[9 21] A key underlying finding from these studies is a decline in routine immunisation rates, especially in the early phase of the pandemic. This decline is indicated by a drop in vaccine coverage and a considerable decline in routine vaccine ordering by national or regional authorities compared with earlier years. However, in other settings, the evidence has been mixed. For example, in countries such as South Korea, there was little to no effect on routine immunisation.[21] Another study of South-East Asia and Western Pacific countries found that the impact of the COVID-19 pandemic on routine immunisation was most pronounced in rural and economically disadvantaged communities.[9] Data for Africa are limited, in part, due to low-quality routine or administrative data. A 2020 study that reported data from 15 African countries found that those with historically high immunisation rates had minimal declines in coverage compared with 2019 rates, while those with lower coverage had larger declines.[22] This study did not include data from The Gambia, a country with historically high immunisation rates. This is a key evidence gap, as the situation in The Gambia may be different from other high performing, but geographically larger countries such as Senegal and Rwanda, which had been included. Additionally, most of the published studies focused on measuring routine coverage, without examining other important and time-sensitive dimensions of immunisation performance, such as the timeliness of vaccination. Timeliness of vaccination, that is, receiving vaccines within the recommended windows and in an age-appropriate manner,[23] is essential to achieving the full benefits of vaccines, along with achieving high coverage. Lastly, most of the studies have been based on cross-sectional surveys, which were conducted early in the pandemic, making it difficult to understand and compare the impact on routine vaccination during the later phases of the pandemic.

To address the identified gaps, the aim of this study was to assess the impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood immunisation in The Gambia. To do this, we used routinely collected data from two health and demographic surveillance system (HDSS) sites. We also examined whether the pandemic impacted the coverage and timeliness of vaccination differently across these two regions in The

Gambia: one with relatively lower coverage and higher untimely vaccination, and the other with relatively better performance.[24] We used HDSS data because they offer a unique opportunity to prospectively or prospectively monitor vital statistics and health indicators, including childhood immunisation over a long period of time.[25] HDSS data are high-quality and population-based, making it an ideal source for studying the impact of the COVID-19 pandemic on routine childhood immunisation. We hypothesise that the COVID-19 pandemic would have led to a statistically significant decrease in routine childhood vaccination coverage and an increase in untimely vaccination (ie, early and delayed vaccinations) in The Gambia. These changes are expected to have been particularly pronounced during the peaks of infections or waves when resources were stretched and disruptions to vaccination services expected to been most severe. We used the birth dose of hepatitis B vaccine (HepB0) and the first dose of pentavalent vaccine (Penta1) as case studies for two reasons. HepB0 is recommended by the WHO to be administered within 24 hours of birth.[26] Therefore, the uptake and timeliness of HepB0 could be significantly affected by disruptions to delivery of immunisation services caused by the COVID-19 pandemic. On the other hand, the administration of Penta1 is the first-time families interact with the immunisation system after the birth period. Studies indicate that delaying or not receiving Penta1 could have a negative impact on subsequent scheduled doses, creating a cascading effect.[27]

METHODS

Study context and COVID-19 timeline

The Gambia, a country located in West Africa, has a population of about 2.5 million people. The median age is 17.8 years, and a national yearly birth cohort of about 90 000 children.[28] More than half of the population lives in urban areas, mainly on the coast.[29] The childhood immunisation programme in The Gambia has been remarkably successful, with routine immunisation coverage rates comparable to those of high-income countries. The country has consistently achieved routine coverage of at least 90% for most childhood vaccines for over a decade prior to the COVID-19 pandemic.[30 31] However, we have previously shown that many children are vaccinated outside of the recommended time frames,[32] especially in districts in the eastern part of the country.[24] The first confirmed case of COVID-19 in The Gambia was identified on 17 March 2020.[33] The evolution of the pandemic and measures taken to control the spread of COVID-19 in The Gambia have been previously described.[34] In brief, in the days following the confirmation of the first case, the government swiftly implemented a series of measures to curb further transmission. These measures included the prohibition of public gatherings, closure of educational institutions including universities, suspension of air travel, closure of land and sea borders, and closure of non-essential businesses. There were three waves of COVID-19 recorded between March 2020 and December 2021. Figure 1A shows the detailed timeline of the COVID-19 related events in The Gambia.

Study design

We used an interrupted time-series (ITS) design to examine the impact of the COVID-19 pandemic on the coverage and timeliness of vaccination in a longitudinal cohort of children born 5 years prior to the pandemic and those born within the initial 2 years of the pandemic. Our choice of an ITS design was justified by the availability of sequential, equally spaced measurements of vaccination coverage and timeliness before and after the COVID-19 pandemic's interruption. This design, with its substantial number of time points, provided a robust framework for isolating the pandemic's specific effect.[35]

Data sources

We used data from the Basse and Farafenni Health and Demographic Surveillance Systems (BHDSS and FHDSS henceforth), which were established about four decades ago. BHDSS and FHDSS are located in eastern and central parts of The Gambia and prospectively follow-up a combined population of 280 000 persons in about 9000 households in over 300 communities (figure 1B).[36] The BHDSS is predominantly rural and located in the part of The Gambia with comparatively lower vaccination coverage and higher rates of delayed vaccination.[24] The FHDSS is predominantly peri-urban and has relatively better coverage and timeliness. The yearly birth cohort is approximately 9000 children in both HDSS. Both sites have supported cutting-edge medical, public health and demographic research since their inception.

Detailed information about the design and methodology of the BHDSS and FHDSS have been described elsewhere,[37] and in online supplemental material. In brief, BHDSS and FHDSS conduct routine surveillance rounds every 4 months to collect health and demographic data from all consenting households in all HDSS communities. Every child born within the HDSS communities is automatically enrolled and followed up by fieldworkers. Information on the date of birth and date of vaccinations is extracted from parent-held vaccination cards during each census round. Any missing information is routinely updated in subsequent rounds for all individuals who have been enrolled. This approach makes HDSS data more robust and potentially better for our purpose than cross-sectional population surveys which although often have high geographical coverage but do not allow for longitudinal follow-up and additionally rely on potentially biased information from caregiver recall to evaluate vaccination coverage.

Data processing

To synthesise adequate evidence regarding the monthly trend in coverage and timeliness well before the pandemic, we included data for 7 years, that is, from all children born from 1 January 2015 to 31 December 2021 in all FHDSS

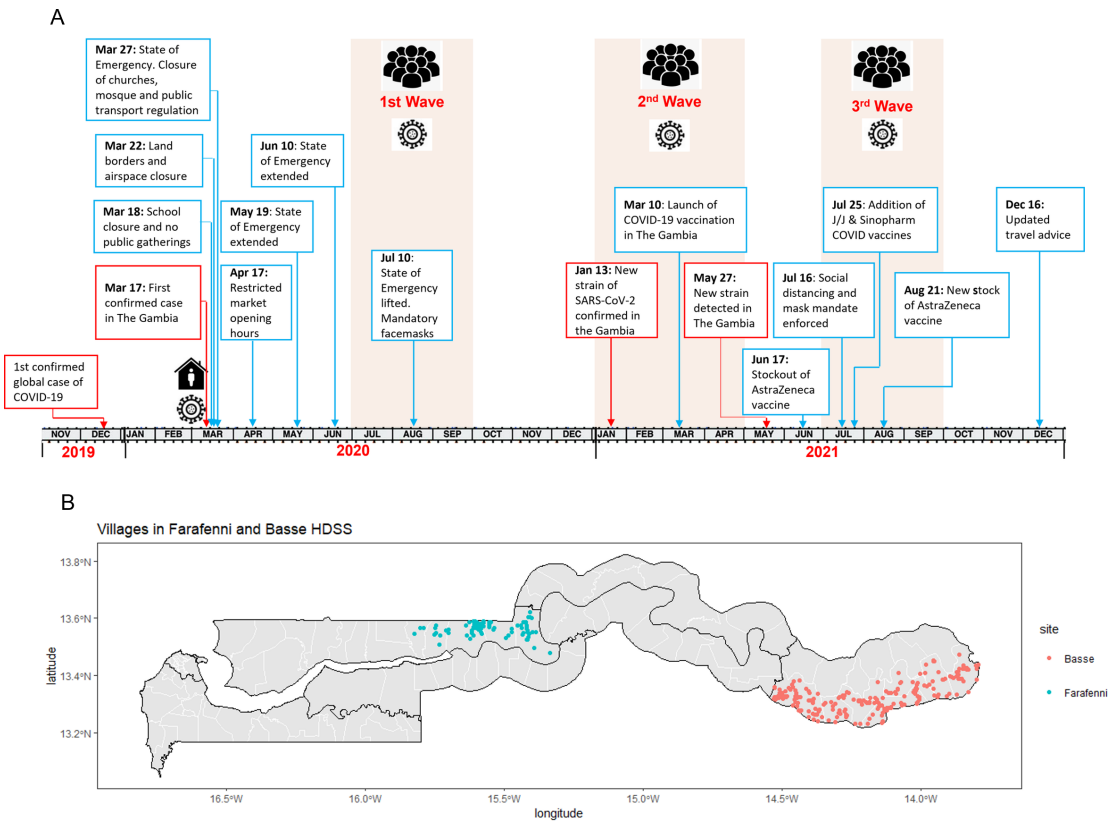


Figure 1 (A) Detailed timeline showing the evolution and measures implemented to control the spread of COVID-19 in The Gambia, March 2020–December 2021. (B) Map of The Gambia showing the location of all the communities covered by the Basse and Farafenni Health and Demographic Surveillance Sites. *In figure 1A, red lines indicate case confirmation, new variants and waves. Blue lines indicate preventive measures implemented by government reduce impact of the pandemic. HDSS, health and demographic surveillance system.

and BHDSS households. The decision to include data for 5 years before and 2 years during the pandemic was also to balance out temporal confounding factors, such as seasonal variations (wet and dry seasons) and monthly birth rate variations. We defined the pre-pandemic epoch as the period from January 2015 to February 2020. The pandemic epoch started in March 2020, when the first case of COVID-19 was confirmed in The Gambia. The time series ends in December 2021. Subsequently, we created 84 birth cohorts, each corresponding to children born in a specific month, starting from January 2015 (cohort 1) to December 2021 (cohort 84). The outcome variable was vaccination coverage and timeliness of vaccination among each of these monthly birth cohorts. Detailed information about the number of eligible children per month and those excluded due to improbable vaccination dates is shown in the online supplemental material

Defining and computing vaccination coverage and timeliness

We defined vaccination coverage as the monthly proportions of children who received the vaccine of interest (HepB0 or Penta1) relative to the respective monthly birth cohorts, regardless of timing. Timeliness was determined based on the accepted vaccination window in The Gambia,[38] in line with recent timeliness studies from The Gambia.[24 32] Age at vaccination (in days) for each vaccine was calculated by finding the difference between vaccination and birth dates for every child. Timely HepB0 and Penta1 was defined as vaccination within 24 hours of birth and between 2 and 3 months of age (ie, 61–90 days), respectively, in accordance with the national vaccination schedule in The Gambia.[38] For children born in BHDSS from September 2019 until December 2021, timely Penta1 was considered as vaccination between 6 and 10 weeks of age (42–70 days). This modified definition for Penta1 in BHDSS was adopted due to the ongoing prospective, cluster-randomised, non-inferiority field trial of an alternative schedule for one dose of pneumococcal conjugate vaccines in this area from September 2019.[39] This trial, conducted in collaboration between the MRC Unit The Gambia at LSHTM and the Gambian Ministry

of Health, administers Penta1 at 6 weeks instead of the usual 2 months. HepB0 and Penta1 vaccinations that were received after the accepted window were considered delayed, whereas Penta1 vaccinations that were received before the accepted window were considered early.

Modelling counterfactual scenario and testing changes due to the pandemic

We performed one-step-ahead simulations to generate the counterfactual scenario after the onset of the pandemic (from cohort 63 or March 2020) using a binomial first-order autoregressive (AR1) time series regression model as shown below in equation (1). This model can be fitted without the $\beta_1 t$ term, but this trend term was included to explicitly test for an overall increasing or decreasing trend in the data. Also, for delayed HepB0, the model that included the explicit trend term performed slightly better than the model without it. The model is given by

$$\begin{aligned} &Y_t \sim Binomial\left(N_t, p_t\right),\ t = 1, \ldots, n = 84, \\ &\text{logit}\left(p_t\right) = \beta_0 + \beta_1 t + \omega_t, \\ &\omega_t | \omega_{t-1} \sim N\left(\rho\omega_{t-1},\ \sigma^2\right), \\ &\omega_1 \sim N\left(0,\ \frac{\sigma^2}{1-\rho^2}\right), \end{aligned} \tag{1}$$

where Y_t is the number of vaccinated children out of a birth cohort of size N_t at time t, p_t is the corresponding underlying true vaccination coverage, β_0 (intercept) and β_1 are regression coefficients and ω_t is an AR(1) term with autoregressive parameter, ρ, and conditional variance, σ^2, accounting for residual serial correlation.

To estimate changes (ie, level change and change in slope) in vaccination coverage and timeliness during the peaks of infections (waves), we extended the base model in (1) to an ITS model.[40] The variable of interest was the proportion of timely, delayed, or early vaccination per month. We assessed changes in the time periods *before* the peaks of the first (T_1 = 63, April–August 2020), second (T_2 = 68, September 2020–March 2021), and third (T_3 = 75, April–August 2021) waves of the pandemic, *as well as* the period *after* the peak of the third wave (T_4 = 80, September–December 2021), relative to the pre-pandemic period (ie, from January 2015 to March 2020). We coded the level changes as indicator variables (ie, D_{t63}, D_{t68}, D_{t75}, D_{t80}), with each variable representing a given time period during which changes are evaluated. For example, D_{t63} is used to assess a level change between the start of the pandemic in The Gambia in April 2020 and the peak of the first wave in August 2020 and is coded 1 within this time period and 0 elsewhere.

Slope changes, assessed using the terms $[t–T_1]D_{t63}$, $[t–T_2]D_{t68}$, $[t–T_3]D_{t75}$ and $[t–T_4]D_{t80}$, were coded as sequentially numbered months during each time period, and 0 before or after.

The baseline monthly trend in coverage and timeliness (time) was coded sequentially throughout the entire study period. The ITS model with a binomial likelihood can be written as

$$\begin{aligned} &Y_t \sim \text{Binomial}\left(N_t, p_t\right),\ t = 1, \ldots, n = 84 \\ &\text{logit}\left(p_t\right) = \beta_0 + \beta_1 t + \beta_2 D_{t63} + \beta_3\left[t - T_1\right] D_{t63} + \beta_4 D_{t68} \\ &+ \beta_5\left[t - T_2\right] D_{t68} + \beta_6 D_{t75} \\ &+ \beta_7\left[t - T_3\right] D_{t75} + \beta_8 D_{t80} + \beta_9\left[t - T_4\right] D_{t80} + \omega_t, \\ &\omega_t \mid \omega_{t-1} \sim N\left(\rho\omega_{t-1}, \sigma^2\right), \\ &\omega_1 \sim N\left(0, \frac{\sigma^2}{1-\rho^2}\right), \end{aligned} \tag{2}$$

where the regression coefficient β_0 estimates the pre-pandemic intercept and β_1—the pre-pandemic slope. The regression coefficients $\beta_2, \beta_4, \beta_6, \beta_8$ are intercept terms measuring immediate level changes in the coverage and timeliness indicators within the segments following the pandemic, and $\beta_3, \beta_5, \beta_7, \beta_9$ measure corresponding changes in slope. As in model (1), ω_t is an AR1 random effect used to capture residual autocorrelation in the model. Both models (1) and (2) were implemented using the integrated nested Laplace approximation approach, in a fully Bayesian framework.[41] We report the ORs and corresponding credible intervals (CIs) of all the regression coefficients.

To provide a comprehensive understanding of delayed vaccination, we calculated the mean number of days children in each birth cohort were delayed for HepB0, in addition to the monthly proportion of delayed vaccination. This mean delay was then compared against the overall average delay for HepB0 vaccination across the entire population and between the pre-pandemic and pandemic periods. All analysis was done in R (R Development Core Team, 2023). We report and compare findings for vaccination coverage, proportion delayed, mean number of days delayed and proportion with early vaccination for the monthly birth cohorts in the pre-pandemic and pandemic periods.

RESULTS

From January 2015 to December 2021, a total of 57 286 children were born in the Basse and Farafenni HDSSs and were eligible for HepB0 and Penta1 vaccination. This number includes 43 428 children from villages within the Basse HDSS and an additional 13 858 children from the Farafenni HDSS. Overall, the coverage of HepB0 vaccination was generally higher than that of Penta1 vaccination throughout the study duration. The proportion of children with delayed HepB0 vaccination was also higher than that of delayed Penta1 vaccination.

Coverage of HepB0 and Penta1

Figure 2A and B illustrate the coverage of HepB0 and Penta1 for monthly birth cohorts during the pre-pandemic and pandemic epochs. The observed HepB0 and Penta1 vaccination coverage declined over time in the pre-pandemic period, but an increasing trend was

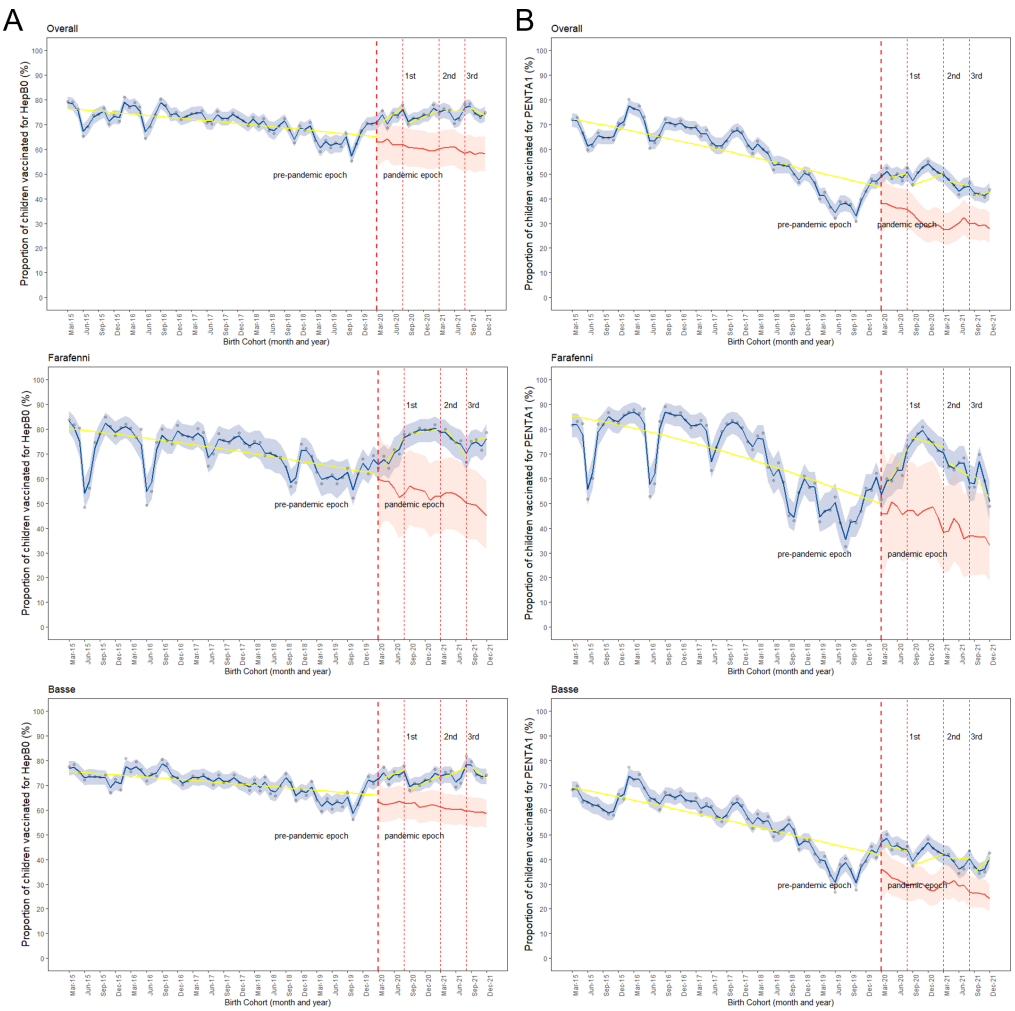


Figure 2 Observed hepatitis B vaccine (HepB0) (A) and pentavalent vaccine (Penta1) (B) coverage, counterfactual scenario and changes (level and slope) due to the pandemic overall, in Farafenni and Basse. *Red-dotted lines indicate when the first case of COVID-19 was confirmed in The Gambia, the peaks of the first, second and third waves. Blue line indicates observed coverage and 95% credible intervals; red line=counterfactual scenario and 95% credible interval; yellow line indicates the change in slope for the proportion of children vaccinated.

observed during the pandemic period, compared with the counterfactual scenario as shown in figure 2A and B.

Overall, the binomial regression model did not find statistically significant differences in the coverage of HepB0 and Penta1 vaccinations between the pre-pandemic period and the period just before the peaks of the first, second, and before and after the third waves of the pandemic, based on level changes. The only exception was the period before and after the peaks of the third wave for HepB0 (table 1 and figure 2A). The likelihood of receiving HepB0 vaccination increased by 83% (OR=1.83, 95% CI 1.06 to 3.14) and 120% (OR=2.20, 95% CI 1.23 to 3.92) in the period before and after the peaks of the third wave, respectively, compared with the pre-pandemic period (table 1). The changes were similar in Farafenni and Basse (figure 2A). In Farafenni, the likelihood of receiving HepB0 increased by 150% (OR=2.54, 95% CI 1.14 to 11.2) during the period preceding the third wave's peak. In the Basse area, there was an increase of 120% (OR=2.21, 95% CI 1.24 to 3.89) following the third wave's peak, compared with the pre-pandemic period (online supplemental table). No statistically significant changes in the slope of the trends were observed overall, or in Farafenni and Basse.

Table 1 Parameter estimates for the likelihood of change in coverage and the proportion of delayed and early hepatitis B vaccine (HepB0) and pentavalent vaccine (Penta1) vaccinations in the pre-pandemic and pandemic periods in The Gambia*

	HepB0			Penta1		
Coverage	**Estimate/OR**	**95% credible interval**		**Estimate/OR**	**95% credible interval**	
Level change						
Before first wave	1.24	0.79	1.93	1.15	0.75	1.74
Before second wave	1.28	0.79	2.01	1.10	0.53	2.19
Before third wave	1.83	1.06	3.14	1.41	0.54	3.41
After third wave	2.20	1.23	3.92	1.17	0.40	3.11
Change in slope						
Pre-pandemic	0.99	0.99	1.00	0.98	0.97	1.00
Before first wave	1.08	0.95	1.23	1.04	0.89	1.20
Before second wave	1.06	0.96	1.15	1.05	0.94	1.18
Before third wave	1.01	0.88	1.16	1.00	0.86	1.17
AFTER third wave	0.95	0.80	1.14	1.05	0.87	1.25
$\hat{\sigma}^{-2}$	31.56	17.99	49.37	11.12	3.74	21.63
$\hat{\rho}$	0.50	0.25	0.72	0.87	0.75	0.96
Delayed						
Level change						
Before first wave	1.25	0.73	2.12	1.60	0.79	3.41
Before second wave	1.65	0.99	2.67	1.13	0.30	3.29
Before third wave	1.46	0.82	2.59	0.96	0.18	3.25
After third wave	**0.53**	**0.29**	**0.97**	0.97	0.16	3.61
Change in slope						
Pre-pandemic	**0.98**	**0.97**	**0.99**	1.00	0.99	1.03
Before first wave	1.05	0.90	1.23	0.90	0.70	1.13
Before second wave	0.94	0.86	1.04	0.94	0.79	1.11
Before third wave	0.81	**0.70**	0.94	0.96	0.76	1.21
AFTER third wave	1.09	0.90	1.32	0.92	0.69	1.22
$\hat{\sigma}^{-2}$	32.25	15.71	60.57	7.21	2.52	13.96
$\hat{\rho}$	0.29	−0.20	0.70	0.78	0.53	0.94
Early						
Level change						
Before first wave				0.54	0.19	1.60
Before second wave				0.30	0.12	0.78
Before third wave				0.49	0.16	1.56
After third wave				0.48	0.14	1.72
Change in slope						
Pre-pandemic				0.99	0.99	1.00
Before first wave				1.01	0.76	1.34
Before second wave				1.12	0.93	1.34
Before third wave				0.99	0.72	1.36
After third wave				0.92	0.60	1.42
$\hat{\sigma}^{-2}$				9.95	5.63	15.87
$\hat{\rho}$				0.38	0.07	0.66

This table summarises the overall estimates. See the online supplemental material for Farafenni-specific and Basse-specific parameter estimates.

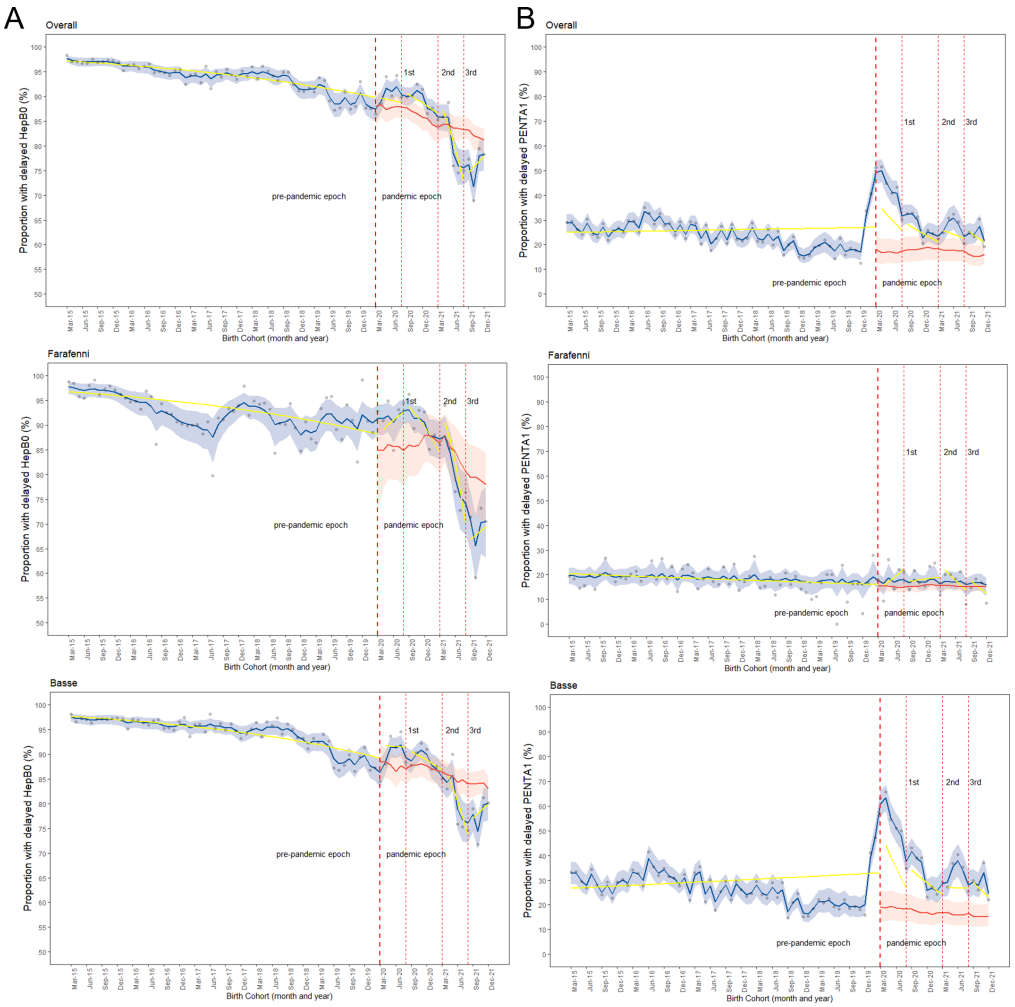


Figure 3 Observed hepatitis B vaccine (HepB0) (A) and pentavalent vaccine (Penta1) (B) delayed vaccination, counterfactual scenario and changes (level and slope) due to the pandemic overall, in Farafenni and Basse. *Red-dotted lines indicate when the first case of COVID-19 was confirmed in The Gambia, the peaks of the first, second and third waves; blue line indicates observed coverage and 95% credible intervals; red line=counterfactual scenario and 95% credible interval; yellow line indicates the change in slope for the proportion of children vaccinated.

The proportion of delayed HepB0 and Penta1

Overall, there was a downward trend in observed delayed HepB0 vaccination in the pre-pandemic period. This trend in delayed HepB0 plateaued in the first year of the pandemic, before a rapid decline in the second year of the pandemic period, compared with the counterfactual scenario (figure 3A). Delayed Penta1 was generally stable (ranging from 20 to 35%) in the pre-pandemic period, with a rapid rise in the months leading up to the pandemic, entirely driven by data from the BHDSS area. However, the monthly proportion of observed delayed Penta1 steadily declined over time (figure 3B).

There were no statistically significant differences in the proportions of delayed HepB0 and Penta1 vaccinations between the pre-pandemic period and the period before the peaks of the first, second, and before and after the third waves of the pandemic, based on level changes (table 1 and figure 3A and B). The only exception was the period after the peaks of the third wave for HepB0 (figure 3A), where the likelihood of delayed vaccination decreased by 47% (OR=0.53, 95% CI 0.29 to 0.97). This finding is consistent with level changes in Farafenni and Basse, where no statistically significant differences were found in the proportion of delayed HepB0 and Penta1

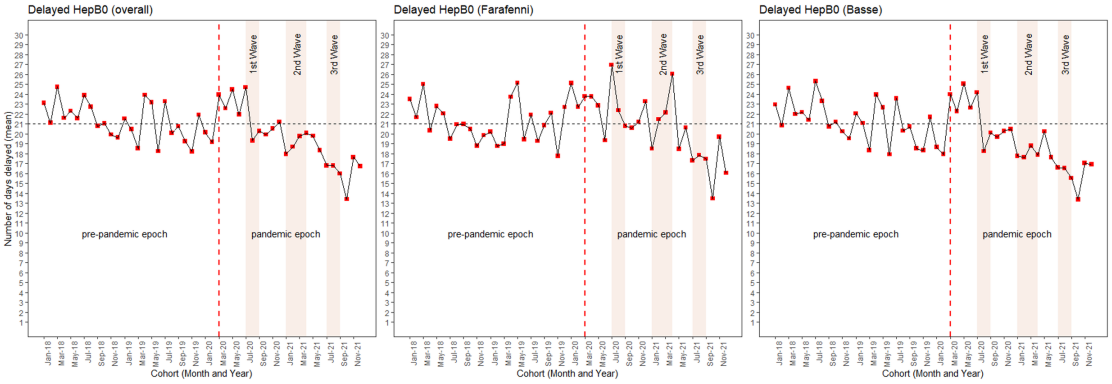


Figure 4 Observed mean number of days with delayed hepatitis B vaccine (HepB0) vaccination per monthly birth cohort in the pre-pandemic compared with the pandemic period overall, in Farafenni and Basse.

vaccinations between the pre-pandemic period and the waves of infections in the pandemic period, based on level change (online supplemental table). Regarding the change in slope of the trend for delayed HepB0, there was a statistically significant decrease in the pre-pandemic period overall and in Basse. Similarly, there was a statistically significant decrease in the slope of the trend for delayed HepB0 for the period before the peak of the third wave, compared with the pre-pandemic period. Overall, the odds of delayed HepB0 decreased by 19% (OR=0.81, 95% CI 0.70 to 0.94) and in Farafenni by 28% (OR=0.72, 95% CI 0.54 to 0.95). The change in slope for Penta1 was not statistically significant (table 1).

Number of days delayed for HepB0

The overall mean number of days with delayed HepB0 was 21 days. In the pre-pandemic period, the monthly mean number of days with delayed HepB0 fluctuated above and below this overall mean. Before the first wave of the pandemic (March–July 2020), the monthly mean number of days delayed for HepB0 was generally above 21 days. However, this gradually decreased below 21 days and has remained so since September 2020 (figure 4). This pattern was mirrored in Basse. In Farafenni, the pattern in the pre-pandemic and pandemic periods was not different.

The proportion of early Penta1

Overall, the trend in the observed monthly proportion of early Penta1 vaccination was stable throughout the pre-pandemic period. This trend was also stable in the pandemic period, but lower when compared with the counterfactual scenario (figure 5). There were statistically significant differences in the observed proportion of early Penta1 vaccinations between the pre-pandemic period and the period before the peaks of the second wave of the pandemic period, both overall and in Farafenni, based on level changes (table 1 and online supplemental table). Compared with the pre-pandemic period, the likelihood of early Penta1 vaccination decreased by 70% (OR=0.30, 95% CI 0.12 to 0.78) and 77% (OR=0.23, 95% CI 0.06 to 0.85) in the period before the peaks of the second wave, overall and in Farafenni, respectively (table 1). Similarly, significant decreases in the proportion of early Penta1

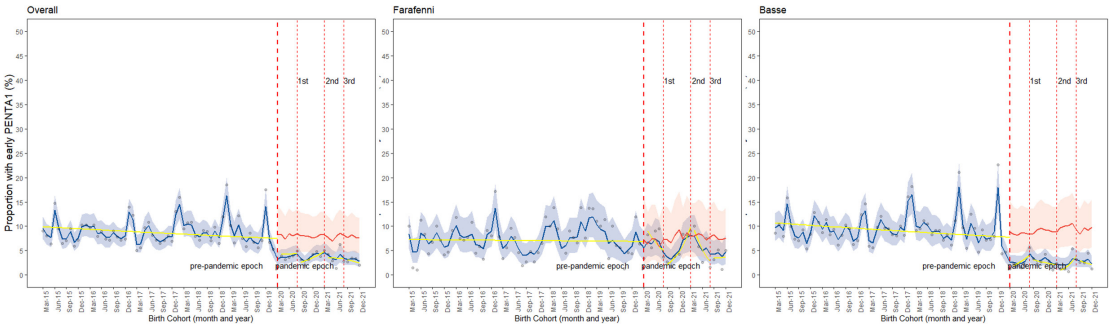


Figure 5 Observed hepatitis B vaccine (HepB0) (A) and pentavalent vaccine (Penta1) (B) early vaccination, counterfactual scenario, and changes (level and slope) due to the pandemic overall, in Farafenni and Basse. *Red-dotted lines indicate when the first case of COVID-19 was confirmed in The Gambia, the peaks of the first, second and third waves; blue line indicates observed coverage and 95% credible intervals; red line=counterfactual scenario and 95% credible interval; yellow line indicates the change in slope for the proportion of children vaccinated.

vaccinations were observed between the pre-pandemic period and the periods before the peaks of the first (OR=0.20, 95% CI 0.05 to 0.76) and third (OR=0.09, 95% CI 0.02 to 0.47) waves of the pandemic period in Basse (online supplemental table). No statistically significant changes in the slope of the trends were observed overall, nor in Farafenni and Basse (online supplemental table).

DISCUSSION

Our study aimed to determine if there were any changes in vaccination coverage and timeliness in The Gambia during the COVID-19 pandemic, compared with before the pandemic. We hypothesised that the COVID-19 pandemic led to a decrease in coverage and an increase in *untimely vaccination* (ie, delayed and early) for subsequent monthly birth cohorts during the pandemic in The Gambia. We found no support for this hypothesis. Rather, our analysis showed that overall, there was no significant change in the coverage of HepB0 and Penta1 vaccinations in the period before the peaks of the first and second waves of the pandemic compared with the pre-pandemic period. These findings diverge from our initial hypothesis, which had anticipated a significant decrease in coverage and an increase in delayed and early vaccination during the pandemic. The findings also differ from previous studies which reported a significant decline in routine vaccination coverage and delays due to the pandemic.[8 10 11 18 20 42] Nonetheless, our findings are consistent with reports showing that African countries with similarly high pre-pandemic immunisation coverage, such as Senegal, Rwanda and Eritrea, have managed to maintain these levels.[22] This is also similar to data from South Korea, which showed that there was little to no effect on routine immunisation due to the pandemic.[21]

Our findings suggest that the Gambia's routine immunisation system was resilient and absorbed the additional shocks imposed on it by the pandemic. This is evident in the maintenance of coverage and timeliness in the first year, and the actual increase in coverage and decrease in delayed and early vaccination in the second year. There are several plausible explanations for these observed findings. The Gambia developed and implemented mitigation strategies to reduce the impact of the pandemic on essential health services. In March 2020, just after the country confirmed its first case of COVID-19, the Ministry of Health developed a guideline for maintaining essential services, including immunisation.[43] This guideline prioritised routine childhood vaccination, specifically, birth dose vaccination, the next dose at 2 months and other subsequent doses.[43] It also mandated the screening and referral for vaccination of eligible children during visits for other services, the continuation of VPD surveillance, and enhanced community sensitisation about the need to continue all scheduled routine vaccinations. The guideline mandated the continuation of immunisation delivery at outreach vaccination sites,[43] a key strategy for delivering routine vaccines that have contributed to the success of the immunisation programme in The Gambia.[44] To reduce waiting time and avoid overcrowding at clinics, some ancillary activities were temporarily suspended during vaccination activities conducted in health facilities (fixed-clinics) until late 2020.[45] These activities included child weight measurement and updating of daily records logbooks, except for recording information on hand-held vaccination cards. Furthermore, in July 2020, before the first wave of the pandemic in The Gambia, the immunisation programme also carried out intensive community sensitisation. They held radio programmes and visited communities to dispel rumours and provide answers to community members' questions about COVID-19. Lastly, the Gambian Expanded Programme on Immunisation (EPI) borrowed routine vaccines from neighbouring Senegal in anticipation of logistical challenges that might deplete their stock. Taken together, these activities likely ensured the maintenance of adequate supply of services and uptake of routine vaccinations during the pandemic.

Our findings are further strengthened by the fact that the mean number of days monthly birth cohorts of children were delayed for HepB0 continuously declined after the onset of the first wave of the pandemic (July 2020 onward) and remained well below the overall mean of 21 days throughout the pandemic period. The WHO target is to ensure all children receive timely HepB0 within 24 hours of birth.[26] However, a consistent decline below 21 days despite the pandemic is a notable improvement, as the mean days delayed for HepB0 historically fluctuated around the overall mean of 21 days before the pandemic. Several factors may explain why the delivery of HepB0 improved despite the pandemic. First, about 2 years prior to the pandemic, The Gambia launched a major initiative to improve the timeliness of HepB0 administration, as hepatitis B virus infection remains endemic in the country, with 15%–20% of the population chronically infected despite high coverage.[46] This initiative strengthened the administration of HepB0 in all health facilities where deliveries occurred by assigning specific health workers to administer HepB0 within the first day of birth. Second, the low number of confirmed COVID-19 cases in the study area compared with urban coastal regions,[47] as well as the lax enforcement of the government stay-at-home order in the study area,[45] may have resulted in a low degree of risk perception. As a result, families may have maintained their health-seeking behaviours related to facility delivery and subsequent receipt of HepB0. Third, the government mandate to prioritise birth doses of vaccines and continue vaccination delivery at outreach vaccination sites during the pandemic could have ensured that services were delivered in a timely manner and available throughout this period.[43] Fourth, in January 2021, the Gambian EPI implemented an electronic immunisation register system called '*MyChild* Solution' across the country.[48] One of the key features of the *MyChild* Solution is the ability to autogenerate predefined indicators and send out SMS messages to valid phone numbers of

parents registered in the system. The EPI programme leveraged the monitoring potential of the solution and, since January 2020 when the system was still being pilot tested, introduced a HepB0 vaccination timeliness indicator which is monitored monthly at the health facility level.[48] Through this solution, facilities throughout the country could monitor timeliness of HepB0 and take data-driven decisions.

Our findings differ in some respects from those of the only other study from The Gambia that has so far explored the impact of the pandemic on vaccination services delivery. In contrast to our findings, the previous study reported reduced clinic visits and vaccination doses administered, particularly for birth doses, for only 3 months after the onset of the pandemic in The Gambia compared with the baseline period.[45] Although the previous study also reported data from BHDSS, which is one of our study sites, slight differences in the objectives and methodology of the two studies could explain the differences in findings. For example, the previous study's outcome measure was the monthly number of clinic attendances and vaccines administered, which may be correlated but different from our study's outcome measure of coverage and timeliness (early and delayed) for each monthly birth cohort. Although the previous study may have found that reported monthly clinic attendance and vaccine doses administered declined, our definition of coverage was based on the cohort of children born for each month. This means that even if monthly visits were briefly reduced in the initial phase of the pandemic, children could still have received doses after their scheduled doses, even outside of their birth month. Furthermore, the previous study was relatively short in duration, as it included data covering only 7 months before the pandemic and 9 months afterwards. Our study included data covering 5 years before the pandemic and 2 years into the pandemic (84 months), and we compared the outcome variables with the temporal trends of multiple years. Due to its short duration, the previous study may not have adequately accounted for confounding factors due to temporal trends occasioned by seasons (wet and dry seasons) and monthly variations in birth rates, unlike our study. Lastly, unlike our study, the previous study did not assess changes in timeliness. Therefore, we cannot ascertain from their data if the decline in clinic visits translated into delayed vaccination or not. Aside from the difference in findings already discussed, the previous study reported that clinic visits and doses administered returned to pre-pandemic levels after a brief decline, which is consistent with our findings. Additionally, the brief decline in clinic visits could explain the brief but rapid rise in the monthly delayed Penta1 vaccination, which was driven entirely by data from BHDSS, their study location.

In our study, we also aimed to understand whether the pandemic impacted the coverage and timeliness of vaccination differently in the BHDSS area (with relatively lower coverage and higher untimely vaccination) compared with the FHDSS area (with relatively better performance). Aside from the brief but rapid rise in monthly delayed Penta1 vaccination in the BHDSS area and the peaks of mean delay for HepB0 above 21 days for monthly birth cohorts observed almost throughout 2020 in the FHDSS area, the impact of the pandemic on coverage and early vaccination was similar in both areas. The minimal difference in the impact of the pandemic in both areas, despite baseline data showing differences in coverage and timeliness in both locations,[24] likely indicates that mitigation measures were implemented in a way that ensured immunisation services in both locations were not negatively impacted by the pandemic.

Our study has some limitations. HDSS communities are observed longitudinally, and households participate in multiple studies where they seldom receive interventions, including vaccinations. This might make them not representative of the general population. Additionally, some individuals or households within the HDSS communities might modify their behaviour (eg, vaccination uptake) because they are aware that they are within a surveillance system—the *Hawthorne effect*.[49] Despite these limitations, our study has several strengths. First, unlike most previous studies, which were based on cross-sectional surveys or electronic immunisation registers, we used routine surveillance data from two large HDSSs. HDSS datasets offer several advantages, including temporal coverage, coverage of underdocumented or often missed communities, and the ability to conduct detailed linkage.[50] Electronic immunisation registers typically only cover individuals who visit immunisation clinics, so they miss out on subpopulations that are unvaccinated or have not interfaced with facilities. HDSSs, on the other hand, conduct a total population census of entire communities, so our findings are likely to reflect the true situation of coverage. Another strength of our study is that our dataset covers multiple years before the pandemic and 2 years into the pandemic. This increases the validity of our findings, as our dataset accounted for temporal trends in seasons, birth rates and other factors that might confound coverage and timeliness estimates. Finally, our study examined both vaccination timeliness and coverage for vaccines given early in infancy. This approach is significant because vaccination timeliness is sensitive to disruptions in services, and studies have shown that not receiving or delaying earlier childhood vaccine doses can potentially initiate a cascading effect, impacting subsequent scheduled doses.[27] While we did not examine doses given in later infancy, we can likely extrapolate the likely impact due to the fact that we used sensitive markers (timeliness and birth doses of vaccines). We do not anticipate widely varying outcomes, given that the only previous study from The Gambia showed that clinic visits for vaccines given in later infancy were minimally impacted.[45]

Author affiliations
[1]Vaccines and Immunity Theme, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, Banjul, The Gambia
[2]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[3]Vaccine Centre, London School of Hygiene and Tropical Medicine, London, UK
[4]WorldPop, School of Geography and Environmental Science, University of Southampton, Southampton, UK
[5]Southampton Statistical Sciences Research Institute, , University of Southampton, Southampton, UK
[6]MARCH Centre, London School of Hygiene and Tropical Medicine, London, UK
[7]Expanded Programme on Immunization, Ministry of Health and Social Welfare, Banjul, The Gambia
[8]Health and Demographic Surveillance System (HDSS), MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, Banjul, The Gambia
[9]Data Management & Architecture, MRC Unit The Gambia a London School of Hygiene and Tropical Medicine, Banjul, The Gambia
[10]Centre on Climate Change and Planetary Health, MRC Unit The Gambia at The London School of Hygiene and Tropical Medicine, Banjul, The Gambia
[11]Centre for Global Health, Charité Universitatsmedizin Berlin, Berlin, Germany

Twitter Oghenebrume Wariri @drwariri and Beate Kampmann @BeateKampmann

Acknowledgements We thank all the parents, guardians, children, and communities in the Farafenni and Basse HDSS for their continuous participation in health and demographic surveillance activities. We are also grateful to the MRC Unit The Gambia at LSHTM's HDSS field team for their tireless work in ensuring the success of the Farafenni and Basse HDSS. We are especially grateful to the data management core of the MRC Unit at LSHTM for their immense contributions to this study. We also thank the EPI programme in The Gambia for their close collaboration on this project.

Contributors Conceptualisation: OW conceptualised this study, with input from CEU, UO, KAM, CG, and BK. Methodology: OW, with inputs from CEU, UO, AS, MS, SF, EE, LS, GS, B-LD, KAM, CG and BK. Project administration: OW, EE, LS, GS and B-LD. Resources: OW, CEU, KAM, BK. Data curation: OW, EE, LS, GS and B-LD. Analysis: OW, with support from CEU. Supervision: CEU, UO, KAM, CG and BK. Writing (original draft): OW. Reviewing manuscript: all authors. All authors approved the content of the final draft of the manuscript and the decision to submit it for publication. OW and CEU had access to the full dataset underlying this work. OW is the guarantor and accepts full responsibility for the work, had access to the data, and controlled the decision to publish

Funding This project is part of the EDCTP2 Programme supported by the European and Developing Countries Clinical Trials Partnership (grant number TMA2019CDF-2734—TIMELY). OW was also supported by an Imperial College London Wellcome Trust Institutional Strategic Support Fund (ISSF) (grant no RSRO_P67869). The Vaccines and Immunity Theme (OW, UO and BK) is jointly funded by the UK MRC and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 Programme supported by the EU (MC UP_A900/1122, MC UP A900/115).

Disclaimer The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The Gambia Government and MRC Unit The Gambia at LSHTM Joint Ethics Committee granted ethical approval for this study (Project ID/Ethics ref: 22786; date: 16 January 2021). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data will be made available on reasonable request through the corresponding author.

ORCID iDs
Oghenebrume Wariri http://orcid.org/0000-0002-7432-8995
Chigozie Edson Utazi http://orcid.org/0000-0002-0534-5310

REFERENCES

1 Bendavid E, Boerma T, Akseer N, *et al*. The effects of armed conflict on the health of women and children. *Lancet* 2021;397:522–32.
2 Chanchlani N, Buchanan F, Gill PJ. Addressing the indirect effects of COVID-19 on the health of children and young people. *CMAJ* 2020;192:E921–7.
3 Grundy J, Biggs BA. The impact of conflict on Immunisation coverage in 16 countries. *Int J Health Policy Manag* 2019;8:211–21.
4 Brolin Ribacke KJ, Saulnier DD, Eriksson A, *et al*. Effects of the West Africa ebola virus disease on health-care utilization - a systematic review. *Front Public Health* 2016;4:222.
5 Masresha BG, Luce R, Weldegebriel G, *et al*. The impact of a prolonged ebola outbreak on measles elimination activities in guinea, Liberia and Sierra Leone, 2014-2015. *Pan Afr Med J* 2020;35:8.
6 World Health Organization. COVID-19 pandemic fuels largest continued backslide in vaccinations in three decades. 2022. Available: https://www.who.int/news/item/15-07-2022-covid-19-pandemic-fuels-largest-continued-backslide-in-vaccinations-in-three-decades [Accessed 19 Jul 2022].
7 Causey K, Fullman N, Sorensen RJD, *et al*. Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study. *Lancet* 2021;398:522–34.
8 Santoli JM, Lindley MC, DeSilva MB, *et al*. Effects of the COVID-19 pandemic on routine pediatric vaccine ordering and administration - United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:591–3.
9 Harris RC, Chen Y, Côte P, *et al*. Impact of COVID-19 on routine Immunisation in South-East Asia and western pacific: disruptions and solutions. *Lancet Reg Health West Pac* 2021;10:100140.
10 Lassi ZS, Naseem R, Salam RA, *et al*. The impact of the COVID-19 pandemic on immunization campaigns and programs: a systematic review. *Int J Environ Res Public Health* 2021;18:988.
11 McDonald HI, Tessier E, White JM, *et al*. Early impact of the coronavirus disease (COVID-19) pandemic and physical distancing measures on routine childhood vaccinations in England, January to April 2020. *Euro Surveill* 2020;25:2000848.
12 Shet A, Carr K, Danovaro-Holliday MC, *et al*. Impact of the SARS-CoV-2 pandemic on routine immunisation services: evidence of disruption and recovery from 170 countries and territories. *Lancet Glob Health* 2022;10:e186–94.
13 Rücker F, Hårdstedt M, Rücker SCM, *et al*. From chaos to control - experiences of healthcare workers during the early phase of the COVID-19 pandemic: a focus group study. *BMC Health Serv Res* 2021;21:1219.
14 World Health Organization. *Guiding principles for immunization activities during the COVID-19 pandemic*. World Health Organization, 2020.
15 World Health Organization. *Maintaining essential health services; operational guidance for the COVID-19 context*. World Health Organization, 2020.
16 World Health Organization. *Framework for decision-making: implementation of mass vaccination campaigns in the context of COVID-19: interim guidance*. World Health Organization, 2020.
17 World Health Organization. Pulse survey on continuity of essential health services during the COVID-19 pandemic. World Health Organization; 2020.
18 Ji C, Piché-Renaud P-P, Apajee J, *et al*. Impact of the COVID-19 pandemic on routine immunization coverage in children under 2 years old in Ontario, Canada: a retrospective cohort study. *Vaccine* 2022;40:1790–8.
19 Carias C, Pawaskar M, Nyaku M, *et al*. Potential impact of COVID-19 pandemic on vaccination coverage in children: a case study of

measles-containing vaccine administration in the United States (US). *Vaccine* 2021;39:1201–4.
20 UK Health Security Agency. Impact of COVID-19 on routine childhood Immunisations: early vaccine coverage data to August 2021 in England in health protection report. UK Health Security Agency; 2021.
21 Yu JH, Jeong HJ, Kim SJ, *et al*. Sustained vaccination coverage during the coronavirus disease 2019 epidemic in the republic of Korea. *Vaccines (Basel)* 2020;9:2.
22 Masresha BG, Luce R, Shibeshi ME, *et al*. The performance of routine immunization in selected African countries during the first six months of the COVID-19 pandemic. *Pan Afr Med J* 2020;37:12.
23 MacDonald SE, Russell ML, Liu XC, *et al*. Are we speaking the same language? an argument for the consistent use of terminology and definitions for childhood vaccination indicators. *Hum Vaccin Immunother* 2019;15:740–7.
24 Wariri O, Utazi CE, Okomo U, *et al*. Mapping the timeliness of routine childhood vaccination in the Gambia: a spatial modelling study. *Vaccine* 2023;41:5696–705.
25 Ye Y, Wamukoya M, Ezeh A, *et al*. Health and demographic surveillance systems: a step towards full civil registration and vital statistics system in sub-Sahara Africa? *BMC Public Health* 2012;12:741.
26 World Health Organization,. *Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination*. Geneva: World Health Organization, 2015.
27 Kiely M, Boulianne N, Talbot D, *et al*. Impact of vaccine delays at the 2, 4, 6 and 12 month visits on incomplete vaccination status by 24 months of age in Quebec, Canada. *BMC Public Health* 2018;18:1364.
28 Worldometer. The Gambia population. 2021. Available: https://www.worldometers.info/world-population/gambia-population/ [Accessed 19 Nov 2021].
29 Gambia Bureau of Statistics. *The Gambia 2013 Population and Housing Census Preliminary Results*. The Gambia Bureau of Statistics, 2013.
30 Wariri O, Edem B, Nkereuwem E, *et al*. Tracking coverage, dropout and multidimensional equity gaps in immunisation systems in West Africa, 2000-2017. *BMJ Glob Health* 2019;4:e001713.
31 Wariri O, Nkereuwem E, Erondu NA, *et al*. A scorecard of progress towards measles elimination in 15 West African countries, 2001-19: a retrospective, multicountry analysis of national Immunisation coverage and surveillance data. *Lancet Glob Health* 2021;9:e280–90.
32 Wariri O, Utazi CE, Okomo U, *et al*. Timeliness of routine childhood vaccination among 12-35 months old children in the Gambia: analysis of national Immunisation survey data. *PLoS ONE* 2023;18:e0288741.
33 Wariri O, Okomo U, Cerami C, *et al*. Establishing and operating a 'virtual ward' system to provide care for patients with COVID-19 at home: experience from the Gambia. *BMJ Glob Health* 2021;6:e005883.
34 Abatan B, Agboghoroma O, Akemoke F, *et al*. Intense and mild first epidemic wave of coronavirus disease, the Gambia. *Emerg Infect Dis* 2021;27:2064–72.
35 Bernal JL, Cummins S, Gasparrini A. Corrigendum to: interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2020;49:1414.
36 Jasseh M, Rerimoi AJ, Reniers G, *et al*. Assessment of the consistency of health and demographic surveillance and household survey data: a demonstration at two HDSS sites in the Gambia. *PLoS One* 2022;17:e0271464.
37 Jasseh M, Gomez P, Greenwood BM, *et al*. Health & demographic surveillance system profile: farafenni health and demographic surveillance system in the Gambia. *Int J Epidemiol* 2015;44:837–47.
38 World Health Organization. Vaccination schedule for Gambia. 2023. Available: https://immunizationdata.who.int/pages/schedule-by-country/gmb.html?DISEASECODE=&TARGETPOP_GENERAL= [Accessed 29 Jan 2023].
39 Mackenzie GA, Osei I, Salaudeen R, *et al*. A cluster-randomised, non-inferiority trial of the impact of a two-dose compared to three-dose schedule of Pneumococcal conjugate vaccination in rural Gambia: the PVS trial. *Trials* 2022;23:71.
40 Dolan SB, Burstein R, Shearer JC, *et al*. Changes in on-time vaccination following the introduction of an electronic immunization registry, tanzania 2016-2018: interrupted time-series analysis. *BMC Health Serv Res* 2022;22:1175.
41 Rue H, Martino S, Chopin N. Approximate bayesian inference for latent gaussian models by using integrated nested laplace approximations. *J R Stat Soc Ser* 2009;71:319–92.
42 Summan A, Nandi A, Shet A, *et al*. The effect of the COVID-19 pandemic on routine childhood immunization coverage and timeliness in India: retrospective analysis of the national family health survey of 2019-2021 data. *Lancet Reg Health Southeast Asia* 2023;8:100099.
43 Ministry of Health The Gambia. *Operational guidelines for maintaining essential RNMCAH services including immunization during the COVID-19 pandemic*. Ministry of Health The Gambia, 2020.
44 Ministry of Health The Gambia. *Draft policy of the expanded programme on immunisation, republic of the Gambia*. Banjul, The Gambia: Ministry of Health The Gambia, 2006: 8.
45 Osei I, Sarwar G, Hossain I, *et al*. Attendance and vaccination at immunization clinics in rural Gambia before and during the COVID-19 pandemic. *Vaccine* 2022;40:6367–73.
46 Kirk GD, Lesi OA, Mendy M, *et al*. The Gambia liver cancer study: infection with hepatitis B and C and the risk of hepatocellular carcinoma in West Africa. *Hepatology* 2004;39:211–9.
47 Department of Strategic Policy and Delivery Office of The President of The Gambia. Social, economic and health impacts of COVID-19 Department of Strategic Policy and Delivery Office of The President of The Gambia; 2020.
48 Sowe A, Namatovu F, Cham B, *et al*. Impact of a performance monitoring intervention on the timeliness of hepatitis B birth dose vaccination in the Gambia: a controlled interrupted time series analysis. *BMC Public Health* 2023;23:568.
49 Rosenberg M, Pettifor A, Twine R, *et al*. Evidence for sample selection effect and hawthorne effect in behavioural HIV prevention trial among young women in a rural South African community. *BMJ Open* 2018;8:e019167.
50 Herbst K, Juvekar S, Jasseh M, *et al*. Health and demographic surveillance systems in Low- and middle-income countries: history, state of the art and future prospects. *Global Health Action* 2021;14:1974676.

Chapter 6: The influence of demand-side and supply-side factors on the timeliness of receiving routine childhood vaccination in The Gambia (Research Paper)

6.1 Overview of Chapter

This chapter addresses the fourth and final objective of my PhD which was; "*To examine the influence of demand-side factors such as individual and family sociodemographic characteristics, as well as supply-side factors such as geographic accessibility to immunisation clinics and the readiness of these clinics to deliver services on the timeliness of receiving routine childhood vaccination in The Gambia*".

This chapter also tests the following hypotheses:

- *The most common factors influencing the timeliness of childhood vaccination in The Gambia will be household factors such as socioeconomic and demographic characteristics, which determine the household's intention or recognition of the need for vaccination.*
- *Factors impacting a household's ability to reach immunisation facilities, such as geographic accessibility or travel time, will have an impact on the timeliness of receiving childhood vaccinations in The Gambia.*
- *Factors determining the readiness of immunisation facilities to deliver appropriate services such as ownership of functional cold storage facility or staffing numbers, will have an impact on the timeliness of receiving childhood vaccinations in The Gambia*.

As of the time of the thesis submission, the research paper that addresses the objective in this chapter was submitted to eClinicalMedicine. The full bibliographic information and intended authorship order is shown below:

Wariri O, Utazi CE, Okomo U, Dotse-Gborgbortsi W, Sowe A, Sogur M, Fofanna S, Murray KA, Grundy C, Kampmann B. (2024) Multi-level determinants of timely routine childhood vaccinations in The Gambia: findings from a nationwide analysis. Submitted Manuscript.

The supplementary material, accompanying the research paper in this chapter is included as **Appendix 10**.

Research paper cover sheet (paper 6)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1509291	**Title**	DR
First Name(s)	Oghenebrume		
Surname/Family Name	Wariri		
Thesis Title	Timeliness of routine childhood vaccination in The Gambia: examining the burden, spatial pattern, determinants and the impact of COVID-19 pandemic		
Primary Supervisor	Chris Grundy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	eClinical Medicine
Please list the paper's authors in the intended authorship order:	Oghenebrume Wariri, Chigozie Edson Utazi, uduak Okomo, Winfred Dotse-Gborgbortsi, Alieu Sowe, Malick Sogur, Sidat Fofanna, Kris A Murray, Chris Grundy, Beate Kampmann.

Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised this study and led it's execution. I collaborated with the Gambia immmunisation programme to update the national facility census and mapping data with additional variables. I cleaned the data, merged datasets, undertook all the analysis, and interpreted the results. I wrote the initial manuscript draft and handled all referencing. I coordinated the pre-submission process, incorporating feedback from all co-authors, and managed the submission process.

SECTION E

Student Signature	[redacted]
Date	20th February 2024

Supervisor Signature	Chris Grundy
Date	21 Feb 2024

6.2 Research Paper

Multi-level determinants of timely routine childhood vaccinations in The Gambia: findings from a nationwide analysis

Authors:

Oghenebrume Wariri MD[1,2,3]*, Chigozie Edson Utazi PhD[4,5], Uduak Okomo PhD[1,6], Winfred Dotse-Gborgbortsi PhD[4,5], Malick Sogur MSc[7], Sidat Fofana MSc[7], Prof Kris A Murray PhD[8¶], Chris Grundy MSc[2¶], Prof Beate Kampmann PhD[1,3,9¶]

Institutions:

1. Vaccines and Immunity Theme, MRC Unit The Gambia a London School of Hygiene and Tropical Medicine, Fajara, The Gambia
2. Vaccine Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom
3. Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom
4. WorldPop, School of Geography and Environmental Science, University of Southampton, Southampton, United Kingdom
5. Southampton Statistical Sciences Research Institute, University of Southampton, Southampton, United Kingdom
6. MARCH Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom
7. Expanded Programme on Immunisation, Ministry of Health and Social Welfare, The Gambia, Banjul, The Gambia
8. Centre on Climate Change and Planetary Health, MRC Unit The Gambia at The London School of Hygiene and Tropical Medicine, Fajara, The Gambia
9. Centre for Global Health, Charité Universitatsmedizin Berlin, Germany

*Corresponding Author

Email: Oghenebrume.Wariri@lshtm.ac.uk

¶Co-senior authors

SUMMARY

Background: Achieving the ambitious goals of the Immunisation Agenda 2030 (IA2030) requires a deeper understanding of factors influencing under-vaccination, including timely vaccination. This study investigates the demand- and supply-side determinants influencing the timely uptake of key childhood vaccines scheduled throughout the first year of life in The Gambia.

Methods: We used two nationally-representative datasets: the 2019-20 Gambian Demographic and Health Survey and the 2019 national immunisation facility mapping. Using Bayesian multi-level binary logistic regression models, we identified key factors significantly associated with timely vaccination for five key vaccines: birth dose of hepatitis-B (HepB0), first, second, and third doses of the pentavalent vaccine (Penta1, Penta2, Penta3), and first-dose of measles-containing vaccine (MCV1) in children aged 12-35 months. We report the adjusted Odds Ratios (aORs) and 95% Credible Intervals (95% CIs) in each case.

Findings: We found that demand-side factors, such as ethnicity, household wealth status, maternal education, maternal parity, and the duration of the household's residency in its current location, were the most common drivers of timely childhood vaccination. However, supply-side factors such as travel time to the nearest immunisation clinic, availability of cold-storage and staffing numbers in the nearest immunisation clinic were also significant determinants. Furthermore, the determinants varied across specific vaccines and the timing of doses. For example, delivery in a health facility (aOR = 1.58, 95%CI: 1.02–2.53), living less than 30 minutes (aOR = 2.11, 95%CI: 1.2–8.84) and living between 30 and 60 minutes (aOR = 3.68, 95%CI: 1.1–14.99) from a fixed-immunisation clinic was associated with timely HepB0, a time-sensitive vaccine that must be administered within 24 hours of birth. On the other hand, children who received Penta1 and Penta2 on time were three- to five-fold more likely to receive subsequent doses on time (Penta2 and Penta3, respectively). Finally, proximity to an immunisation facility with functional vaccine cold-storage was a significant supply-side determinant of timely MCV1 (aOR = 1.4, 95%CI: 1.09–1.99).

Interpretation: These findings provide valuable insights for programme managers and policymakers. By prioritizing interventions and allocating scarce resources based on these identified determinants, they can maximize their impact and ensure children in The Gambia receive timely vaccinations throughout their first year of life, contributing to IA2030 goals.

Funding: This project is part of the EDCTP2 Programme supported by the European and Developing Countries Clinical Trials Partnership (grant number TMA2019CDF-2734 – TIMELY).

RESEARCH IN CONTEXT

Evidence before the study

On January 14, 2024, we searched PubMed for studies on determinants of childhood vaccination timeliness in Low- and Middle-Income Countries. We used a broad combination of terms related to "childhood", "infant", "vaccination", "immunisation", "timeliness", "delay", "age-appropriate", “drivers”, "determinants", “LMICs”, and “Africa South of the Sahara” without language or date restrictions. While we found several studies exploring the determinants of childhood vaccination timeliness in LMICs, they primarily focused on demand-side factors, such as sociodemographic characteristics of children, mothers, and households. Only a limited number of studies examine supply-side factors such as geographic access to vaccination services or broader immunisation system barriers. Moreover, none of the studies were guided by a robust theoretical model, such as a conceptual framework. This lack of theoretical grounding hindered a comprehensive understanding of the intricate interplay between demand and supply-side factors and their potential impact on vaccination timeliness.

Added value of this study

We conducted a comprehensive analysis of both demand-side and supply-side factors influencing the timeliness of receiving routine childhood vaccination. We analysed diverse vaccines administered at various points in infancy and utilized robust conceptual frameworks, thus, the study offers a deeper understanding of this complex issue. Crucially, our study highlights that while demand-side factors influencing households' recognition of the need to seek vaccination services were leading determinants of timely vaccinations, supply-side factors such as travel time to vaccination facilities, functional cold chain availability, and staffing levels at facilities also played a significant role**.**

Implications of all the available evidence

The findings of this nationally-representative analysis offer crucial insights for governments, immunisation programme managers and service providers regarding the complex and multi-level factors influencing childhood vaccination timeliness. Through strategic prioritization of interventions and allocation of limited resources to address both demand and supply-side determinants, immunisation programmes can ensure that children receive vaccinations at the optimal time, as recommended, to achieve maximum protection.

INTRODUCTION

While the World Health Organization's (WHO) Expanded Programme on Immunisation (EPI) has achieved remarkable success in improving routine vaccine coverage globally, inequalities in the uptake of childhood vaccines persist.[1,2] Furthermore, vaccine-preventable diseases (VPDs) still claim the lives of approximately 1.5 million children annually.[3] The persistence of VPDs despite high vaccine coverage underscores the importance of understanding vaccination not only in terms of coverage but also in terms of timeliness.[4] The growing consensus is that focusing solely on high vaccination coverage, a simple measure of the proportion of vaccinated individuals, is no longer adequate, as timely vaccination also plays a crucial role in disease prevention. Achieving global eradication of measles demands a minimum of 95% immunity in every birth cohort, rather than an average coverage of 95% across the entire population.[5] This emphasises the importance of timely vaccination, which involves ensuring that children receive their doses at the recommended time to provide maximum protection.[6] Unfortunately, timely vaccination has not been a priority in many low- and middle-income countries (LMICs). In The Gambia, despite relatively high routine vaccination coverage similar to that achieved in many high-income countries,[7,8] multiple studies,[9-11] including our previous research,[12,13] have revealed significant gaps in the timeliness of children's vaccinations. It is evident that a high coverage does not necessarily ensure the timely administration of vaccines. This suggests that, while achieving high vaccination coverage rates is important, it is equally crucial to ensure timely vaccinations.

Launched by the WHO, the Immunisation Agenda 2030 (IA2030) is an ambitious global strategy for the next decade to ensure everyone, everywhere has equitable access to life-saving vaccines.[2] To achieve this, immunisation programme managers and policymakers need a comprehensive understanding of the factors influencing non-vaccination and under-vaccination, including vaccination timeliness. Although extensive research has explored the determinants of vaccination coverage in LMICs,[14-17] studies on the determinants of timeliness remain limited in scope and depth,[18,19] creating a substantial blind spot. While numerous studies, including systematic reviews, have established links between various individual, household or community-level factors and vaccination coverage in different LMIC settings,[15-17,20] research on drivers of vaccination timeliness lags. Most existing studies have focussed on child, maternal, and household sociodemographic characteristics,[21-25] neglecting the influence of broader, multi-level quantitative supply-side factors. To our knowledge, only few studies have examined community-level factors such as access to vaccination services[26] or immunisation system barriers to timely childhood vaccinations.[19] The existing research on timeliness often focuses on limited number of vaccines and vaccination timepoints,[27,28] neglecting the diversity of vaccines administered at various periods throughout the first year of life. There is evidence to suggest that determinants of effective vaccination may differ depending on the timing of the dose,[29] with birth being a particularly vulnerable period and

coverage in later infancy potentially influenced by different factors. Furthermore, no in-depth quantitative studies have yet attempted to measure the determinants of vaccination timeliness based on a robust theoretical model such as a conceptual framework. This lack of a comprehensive theoretical foundation hinders an understanding of the complex interplay between various factors and their potential impact on timely vaccination.

To ensure timely childhood vaccinations, addressing the identified knowledge gaps is crucial. By conducting research that encompasses broader quantitative factors, diverse vaccines given during infancy, and utilising robust theoretical frameworks, we can better understand the complex dynamics that influence timely childhood vaccination. In this study, we examined the determinants of timely routine childhood vaccines in The Gambia, focusing on those scheduled within the first year of life (i.e., birth, 2, 3, 4, and 9 months). Specifically, we included the birth-dose of hepatitis-B vaccine (HepB0), the first, second, and third doses of the pentavalent (i.e., Diphtheria, Pertussis, Tetanus, Hepatitis B and Haemophilus influenzae type B) vaccine (Penta1, Penta2, and Penta3), and the first dose of the measles-containing vaccine (MCV1).We examined broader, multi-level quantitative factors that determine the recognition of the need for vaccination or demand-side factors. We also examined quantitative factors that impact a household or community's ability to access immunisation facilities and the readiness of facilities to deliver timely vaccinations (i.e., supply-side factors).

METHODS

Conceptual framework and included variables

Our analysis was based on the integration of two complementary frameworks: the 'three-delays model' proposed by Thaddeus and Maine,[30] to understand drivers of maternal mortality, and the framework developed by Philips et al[14] to examine determinants of effective vaccine coverage. Both frameworks propose three levels of factors influencing the receipt of care/vaccination: those determining the intention or recognition of the need for care/vaccination (i.e*., level 1 factors*); those impacting a household's ability to access health facilities (i.e*., level 2 factors*); and those that determine the readiness of health facilities to deliver appropriate and timely services (i.e., *level 3 factors*). Philips et al[14] further classifies the *level 1 factors* as demand-side factors, while the *level 2 and level 3 factors* are considered supply-side factors (Figure 1).

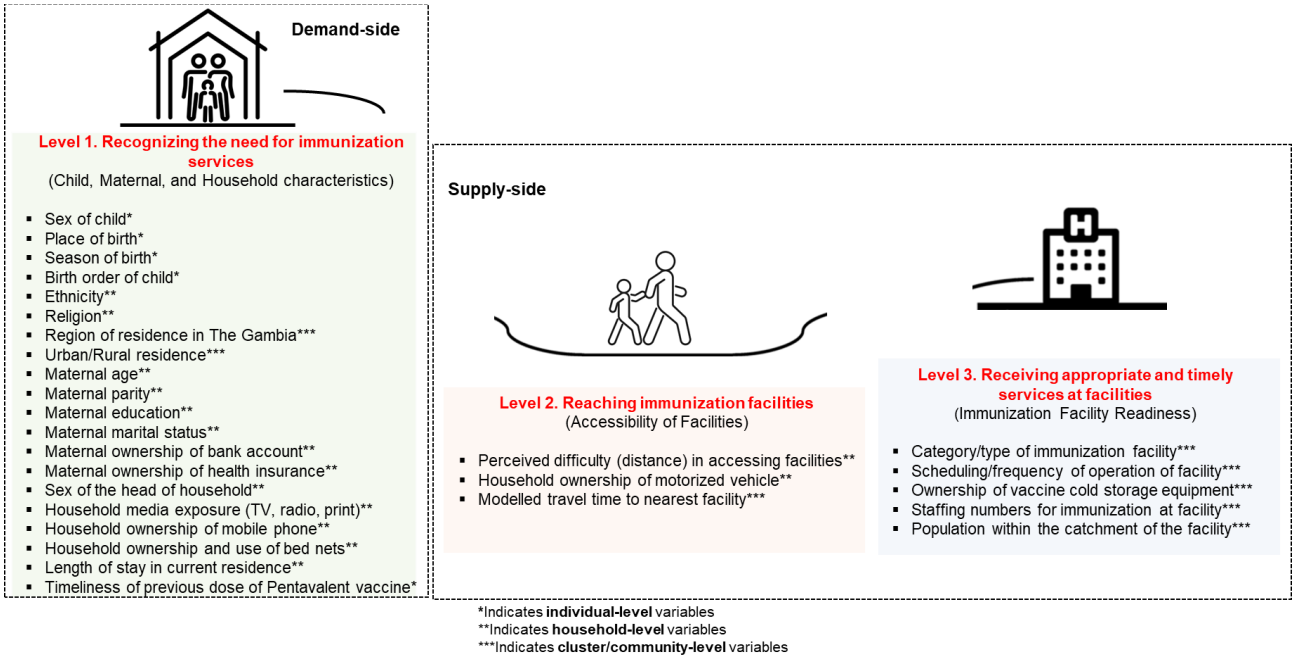


Figure 1: Outcome variables and groups of level 1, level 2 and level 3 factors considered in the study, classified according to the conceptual frameworks adopted.[14,30]

Level 1 factors typically include socioeconomic and demographic variables. Variables such as travel time to health facilities, perceived distance to the facility, and ownership of a motorized vehicle are considered *level 2 factors*. *Level 3 factors* include the organization of the clinics, scheduling of services, staffing numbers, and the population within the catchment area of a facility, which can impact waiting times for services as shown in literature.[31,32] This combined framework allowed us to comprehensively analyse the drivers of timely vaccination at the individual, household, and community/cluster levels.

The inclusion of variables in this analysis was guided by evidence from the literature on drivers of timely or effective vaccination,[14-16,18-20] expert knowledge, and data availability. The complete list of included explanatory variables and their coding are provided in Figure 1 and Table S1 of the supplementary appendix respectively.

Data sources and data collection

For each child aged 12–35 months in the 2019–20 Gambia Demographic and Health Survey (GDHS),[33] we extracted and processed data on the outcome variables—timely HepB0, Penta1, Penta2, Penta3, and MCV1—and all the variables related to *level 1 factors*. We also extracted and processed variables related to *level 2 factors* and the geographical coordinates (latitude and longitude) of the selected cluster from the 2019–20 GDHS. Detailed information about the methodology of the 2019-20 GDHS is available in the supplementary appendix.

To estimate the geographic accessibility of immunisation facilities (*level 2 factors*) and the factors influencing their readiness to deliver appropriate and timely services (*level 3 factors*), we utilised

data from the national immunisation facility mapping conducted by The Gambia EPI programme in 2019 (see supplementary appendix for further details). This comprehensive dataset, temporally aligned with the 2019–20 GDHS, included: geospatial data (latitude and longitude) of all immunisation sites; category of facility (fixed or outreach site); ownership of functional vaccine cold storage; and population within the facility catchment area, defined using a travel-time least-cost-path model. To ensure we had data on other *level 3 factors* not already captured, we collaborated with The Gambia EPI to update the national immunisation facility mapping dataset with additional variables, including the number of times each facility is open per month and staffing levels for service provision. Detailed information about how children within DHS clusters were linked to the nearest facility, along with its qualities (i.e., the facility characteristics), is provided in the supplementary appendix.

Defining and computing the outcome variables

We assessed vaccination timeliness based on established windows in The Gambia's routine vaccination schedule, which includes five appointments in the first year (birth, 2, 3, 4, and 9 months).[34] For each vaccine, we calculated the age of the child at vaccination (in days) by subtracting their birth date from the date they received the vaccine. Timely HepB0, Penta1, Penta2, Penta3, and MCV1 was defined as vaccination within 24 hours of birth, between 61 – 90 days (i.e., 2 months), 91 – 120 days (i.e., 3 months), 121 – 150 days (i.e., 4 months) and 271 – 300 days (i.e., 9 months) respectively, in accordance with the national vaccination schedule in The Gambia.[34] Any vaccination outside these windows was classified as untimely, regardless of whether it was received too early or too late. To evaluate a child's ability to consistently receive the multi-dose Penta vaccine (i.e., Penta1, 2 and 3) according to the recommended schedule, we created a timely “All Penta” variable. This composite variable indicates whether all three Penta doses were received within the recommended timeframe. Any child receiving at least one dose outside the window was considered untimely for this composite variable.

Estimating geographic accessibility

Travel time from each 2019-20 GDHS cluster to the nearest immunisation clinics was employed as the primary indicator for assessing geographic accessibility. Travel time was chosen as it encompasses various factors, including elevation, barriers, road network, and travel speed, which collectively influence geographic accessibility more accurately than Euclidean or straight-line distances.[35] Travel times were modelled as the least cost path over an impedance surface. Motorised and walking speeds on roads were assigned conservatively using calibrated speed limits (S3 Table), based on travel time studies conducted in similar African context.[36,37] Travel time was generated at 1 km by 1 km resolution and extracted using the corresponding cluster locations from the 2019–20 GDHS. Median travel times were extracted within 5 km and 2 km buffer zones for rural and urban clusters, respectively, to account for the deliberate displacement of cluster

locations applied in the DHS methodology to ensure respondents' confidentiality.[38,39] Detailed information about the modelling approaches and data sources used in the process is shown in the supplementary appendix.

Bivariate and multivariate multi-level modelling of the determinants of timely vaccination

We began with bivariate analyses, fitting simple binary logistic regression models, for each outcome with one variable (covariate) at a time. These "reduced" models mirrored the full, multi-level model but included only the individual level. This simplified analysis allowed us to understand the independent association of each covariate on the outcome without interference from other covariates.

To address multicollinearity in the multivariate analyses, we computed generalized variance inflation factors (GVIFs) [40] for each covariate/outcome combination. We excluded variables with high GVIFs (> 2, ensuring comparability across covariates as recommended by Fox & Monette[40]) or those showing inconsistent significant associations between the bivariate and multivariate analyses (a common sign of undetected multicollinearity). For these preliminary analyses, we used the traditional frequentist approach.

For the full multivariate analysis, we employed a Bayesian multi-level random intercept logistic regression model to estimate the relationships between timely vaccination and the covariates, accounting for individual, household, cluster and stratum-level variations. The multi-level random intercept logistic regression model used in the multivariate analysis is described as follows. Let y_{ijkl} denote the binary response, representing vaccination timeliness (HepB0, Penta 1, Penta 2, Penta 3, All Penta, or MCV1) for the ith child in household j, cluster k and stratum l, and p_{ijkl} the corresponding probability of timely vaccination. The model is given by

$$y_{ijkl} \sim \text{Binomial}(1, p_{ijkl}), i = 1, \dots, n_{jkl}, j = 1, \dots, n_{kl}, k = 1, \dots, n_l, l = 1, \dots, L,$$

$$\text{logit}(p_{ijkl}) = \beta_0 + \sum_{p=1}^{r_1} \beta_p^{ind} x_{pijkl} + \sum_{p=1}^{r_2} \beta_p^{house} x_{pjkl} + \sum_{p=1}^{r_3} \beta_p^{clust} x_{pkl} + \delta_{jkl}^{house} + \delta_{kl}^{clust} + \delta_l^{strat},$$

$$\delta_{jkl}^{house} \sim N(0, \sigma_{house}^2), \delta_{kl}^{clust} \sim N(0, \sigma_{clust}^2), \delta_l^{strat} \sim N(0, \sigma_{strat}^2), \quad (1)$$

Here r_1, r_2 and r_3 represent the numbers of individual, household, and cluster-level covariates (see figure 1), respectively. β_0 is the overall intercept and β_p^{ind}, β_p^{house} and β_p^{clust} are regression coefficients or fixed effects corresponding to the covariates x_{pijkl}, x_{pjkl} and x_{pkl} respectively. δ_{jkl}^{house}, δ_{kl}^{clust} and δ_l^{strat} are the household, cluster and stratification random effects with variances σ_{house}^2, σ_{clust}^2 and σ_{strat}^2 respectively. The inclusion of clustering and stratification as random effects in the model aims to account for the complex design used in DHS surveys [41]. This approach is an alternative to incorporating survey weights directly into the model. Notably, no interaction terms were included in the model.

In the bivariate and multivariate analyses, we calculated crude (unadjusted) and adjusted odds ratios (cORs and aORs) respectively as the exponentiated estimates of the fixed effects, along with their corresponding 95% confidence intervals (CIs) or credible intervals (CIs) to assess the significance of the covariate-timely vaccination associations. In both analyses, covariates with 95% CIs not containing the value 1 were considered to have significant associations with timely vaccination. Data cleaning, validation and analysis were carried out using the R programming language [42], and the R-INLA package [43].

Model estimation and evaluation of predictive ability

We placed a non-informative prior $N(0, 10^{-3})$ on all regression coefficients and an informative $\text{Gamma}(0.1, 0.1)$ prior with a mean of 1 and variance 10, on the precisions of the random effects. This choice ensured they were well-estimated, especially σ_{house}^{-2} whose estimation can often be affected by small sample sizes at this level. [44] We tested different prior specifications for the variance parameters in model (1) but observed no significant changes in the estimated fixed effects. Similarly, including or excluding the household level in the model didn't meaningfully alter the fixed-effect estimates.

To assess the models' abilities to predict timely vaccination, we calculated the area under the receiver operating characteristic curve (AUC). This metric is defined by plotting sensitivity against 1 minus specificity (sensitivity and specificity in our context relate to the proportions of timely vaccination and untimely vaccination correctly classified by the fitted models). AUC scores close to 1 indicate excellent discrimination, with 0.5 representing chance performance. [45] Furthermore, we used variance partitioning coefficients (VPC) to examine how much of the total variance in the outcome variable (after accounting for the effects of covariates) can be attributed to different levels of the model's hierarchy.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

RESULTS

In the bivariate analysis, all variables were significantly associated with the timely receipt of at least one of the vaccine-dose considered, except six level 1 variables (ownership of bed nets, sex of household head, maternal health insurance, maternal age, child's birth order, and season of birth). This finding further justifies the decision to include all the variables in our analysis. The figures showing the unadjusted ORs and corresponding 95% CIs from the bivariate analyses can be found in the supplementary appendix as Fig S6 – S11. The adjusted ORs observed in the multivariate analyses are presented below. Please refer to Table 1 below for the reference categories of all the covariates in both the bivariate and multivariate analyses.

Table 1: The reference categories of all the determinants of timely vaccination included in the bivariate and multivariate regression analysis

	Covariate (variable)	**Reference category**
1.	Sex of child	Female
2.	Place of birth	Home
3.	Season of birth	Wet (June – October)
4.	Birth order	>5
5.	Ethnicity	Non-Gambian
6.	Religion	Christianity
7.	Region*	Other regions (Kuntaur, Janjanbureh & Basse)
8.	Urban/Rural	Rural
9.	Maternal age	<=19
10.	Timeliness of previous Penta dose	Untimely
11.	Parity	≥4
12.	Maternal education	No education
13.	Marital status	Never in union
14.	Maternal bank account	No
15.	Maternal health insurance	No
16.	Sex of household head	Female
17.	Household size	Large (9 or more)
18.	Wealth index	Poor
19.	Household media exposure	Not exposed to media
20.	Household own mobile phone	No
21.	Household own bed nets	No
22.	Length of stay	<1 year
23.	Distance to clinic as an issue?	Big problem
24.	Household own motorized vehicle	No
25.	Travel time - multimodal	60 mins and above
26.	Nearest clinic type	Outreach Site
27.	Nearest clinic open weekly	No
28.	Nearest clinic has cold store	No
29.	Nearest clinic vaccination staff	One (1)
30.	Catchment pop around nearest clinic	High
31.	Service availability & readiness	low (0-1)

*Note: Greater Banjul consist of Banjul and Kanifing Municipality. “Other regions” are the three regions located in the eastern part of The Gambia.

Determinants of timely receipt of HepB0 and MCV1

The aORs and corresponding 95% CIs from the multivariate analyses for determinants of timely HepB0 and MCV1 are plotted in Figure 2. For timely HepB0 vaccination, variables that had significant positive associations (i.e. significantly increased the odds of timely vaccination) were: place of birth, region of residence, maternal parity, household size, length of stay in current residence, and travel time to the nearest fixed health facility. On the other hand, household wealth status and ownership of vaccine cold storage at nearest facility were the variables that had significant positive associations with timely MCV1.

Children born in a health facility had 58% (aOR = 1.58, 95%CI: 1.02–2.53) higher chance of receiving timely HepB0 compared to those born at home. Compared to children from “other regions” (Kuntaur, Janjanbureh & Basse), those in Greater Banjul, Brikama and Kerewan were

281% (aOR = 3.81, 95%CI: 1.13–13.86), 275% (aOR = 3.75, 95%CI: 1.20–11.80) and 386% (aOR = 1.58, 95%CI: 1.02–2.53) more likely of receiving timely HepB0 respectively. Children born to mothers with 1-3 previous births (parity) were 62% more likely to receive timely HepB0 compared to those born to mothers with 4 or more previous births (aOR = 1.62, 95%CI: 1.02–2.55). Additionally, children from households who had resided in their current home for 1-3 years were 143% more likely to receive timely HepB0 compared to those who had lived there for less than a year (aOR = 2.43, 95%CI: 1.02–6.52). Children who lived less than 30 minutes and those who lived between 30 and 60 minutes from a fixed health facility had a 111% (aOR = 2.11, 95%CI: 1.2–8.84) and 268% (aOR = 3.68, 95%CI: 1.1–14.99) higher chance of receiving timely HepB0, respectively, compared to children who lived more than 60 minutes away (Figure 2).

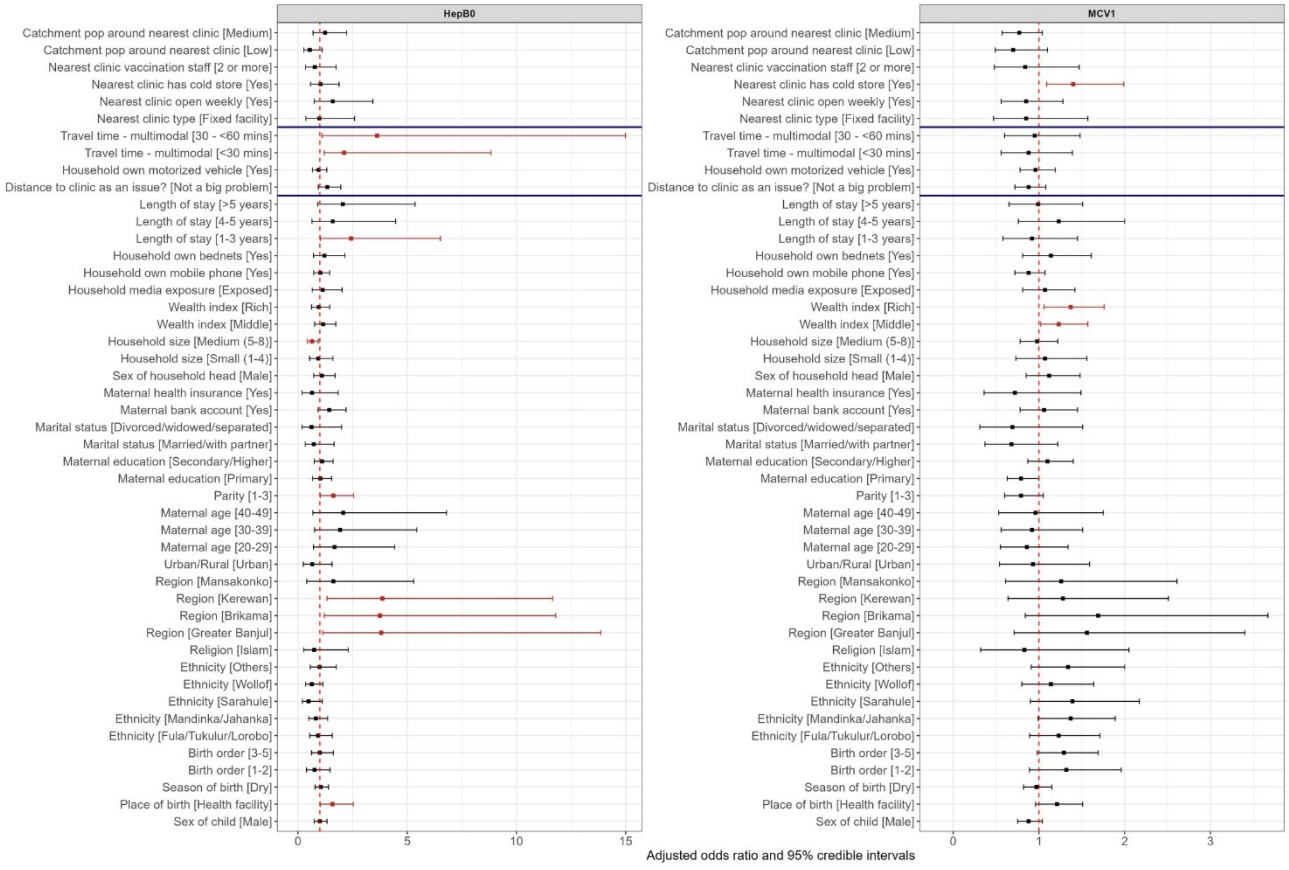


Figure 2: Adjusted odds ratio and corresponding 95% credible interval plots for determinants of timely birth-dose of hepatitis B (HepB0) and first-dose measles containing vaccine (MCV1). **Note:** The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Compared to children from poor households, children from middle-income households had a 23% higher likelihood (aOR = 1.23, 95%CI: 1.02–1.57) of receiving timely MCV1 vaccination (Figure 2). Similarly, children from wealthy households had a 37% higher likelihood (aOR = 1.37, 95% CI: 1.06–1.76) of receiving timely MCV1 vaccination. Children living near an immunisation facility equipped with a functional vaccine cold store had a 40% higher chance (aOR = 1.4, 95%CI: 1.09–

1.99) of receiving timely MCV1 vaccination compared to children whose closest facility lacked a cold store.

Determinants of timely receipt of Penta1, Penta2, Penta3 and "All Penta"

Determinants of timely multi-dose pentavalent vaccination uptake varied across doses. The following variables had significant associations with timely Penta1 vaccination: ethnicity and length of stay in the current residence. For timely Penta2 vaccination, the variables that showed significant associations were timeliness of receiving Penta1 and staffing numbers providing services in the nearest immunisation facility. Similarly, the variables that had significant associations with timely Penta3 were timeliness of receiving Penta2, ethnicity, maternal parity, maternal education, and household wealth status (Figure 3). Children belonging to specific Gambian ethnic groups were significantly more likely to receive timely Penta1 vaccination compared to non-Gambian children. Notably, Mandika/Jahanka children had a 59% higher chance, followed by Fula/Tukular/Lorobo (70%), Wollof (73%), and Sarahule (102%). Additionally, children residing in their homes for 1-3 years were 77% more likely, while those residing for 4-5 years were 138% more likely to receive timely Penta1 compared to those who had lived there for less than a year.

Figure 3: Adjusted odds ratio and corresponding 95% credible interval plots for determinants of timely first, second and third dose of pentavalent vaccine (Penta1, Penta2 and Penta3). **Note:** The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Similar to the pattern observed in Penta1, children of Fula/Tukular/Lorobo ethnicity were 44% more likely to receive timely Penta3 compared to non-Gambian children. The timeliness of receiving previous doses of the pentavalent vaccine played a crucial role in determining the likelihood of receiving subsequent doses on time. Children whose Penta1 was timely were significantly more likely to receive timely Penta2, with more than threefold higher chance (354%) compared to those with untimely Penta1 (aOR = 4.54, 95%CI: 3.49–6.1). This pattern was further amplified for Penta3, where children with timely Penta2 demonstrated a fivefold (539%) increase in the likelihood of timely Penta3 uptake compared to those with untimely Penta2 (aOR = 6.39, 95% CI: 5.73–7.12) (Figure 3). Beyond the crucial influence of previous pentavalent vaccine timeliness, several level 1 factors (i.e., demand-side) emerged as significant predictors of timely Penta3. Children born to mothers with 1-3 previous births (parity) compared to those with four or more children, those whose mothers had secondary or higher education compared to those with no formal education and those from middle-income families compared to those from poor households had 62%, 31% and 57% significantly higher chance of timely Penta3 respectively.

All covariates that determined a child's ability to consistently receive all three doses of pentavalent vaccine (i.e., Penta1, 2 and 3) in a timely manner, were *level 1 factors* (Figure 4). Male children, children whose mothers had a secondary or higher education, those with Gambian parents, and those from middle-income families had a higher chance of receiving timely "All Penta" compared to female children, those whose mothers had no formal education, those born to non-Gambian parents and those from poor households. Specifically, male children had a 19% higher chance (aOR = 1.19, 95% CI: 1.01-1.4), children whose mothers had a secondary or higher education had a 24% higher chance (aOR = 1.24, 95% CI: 1.08-1.56), and children from middle-income families had a 49% higher chance (aOR = 1.49, 95% CI: 1.17-1.9).

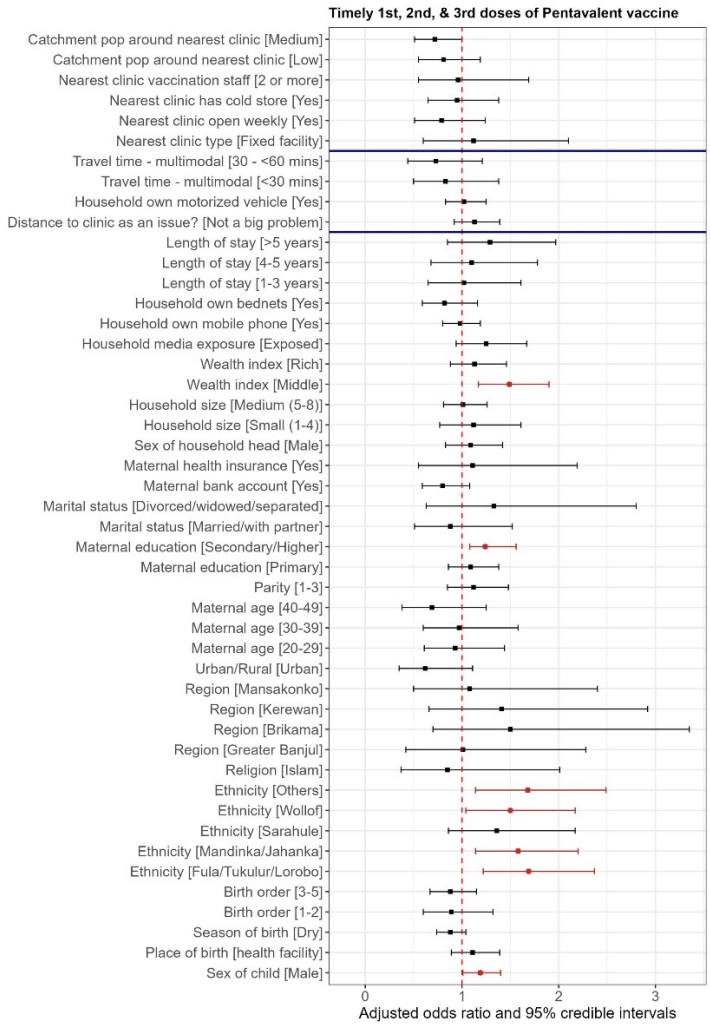


Figure 4: Adjusted odds ratio and corresponding 95% credible interval plots for determinants of consistent timely all doses of pentavalent vaccine (i.e., Penta1, Penta2 and Penta3). **Note:** The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Summary of determinants of timely vaccination and predictive ability of the models

The summary of the estimated relationship between the covariates and timely vaccination for all the vaccines examined is shown in Figure 5. Level 1 factors were the commonest determinants across all the vaccines, however, level 2 and 3 factors were also significant. Ethnicity (Penta1, Penta3 and All Penta) and household wealth status (Penta 3, MCV1 and All Penta) were significant across three of the vaccines each compared to maternal parity, maternal education and length of stay in current residence which were significant across two vaccines. The timeliness of previous Pentavalent vaccine was a significant predictor for all subsequent doses. The plots of predictive ability of the models (AUC) and the proportion of the total residual variation attributed to different levels of the model's hierarchy (VPC) are shown in supplementary appendix (Fig S4 and S5). the AUC scores for the six vaccines examined range between 0.76 and 0.90, showing that all the fitted models had good discriminatory power.

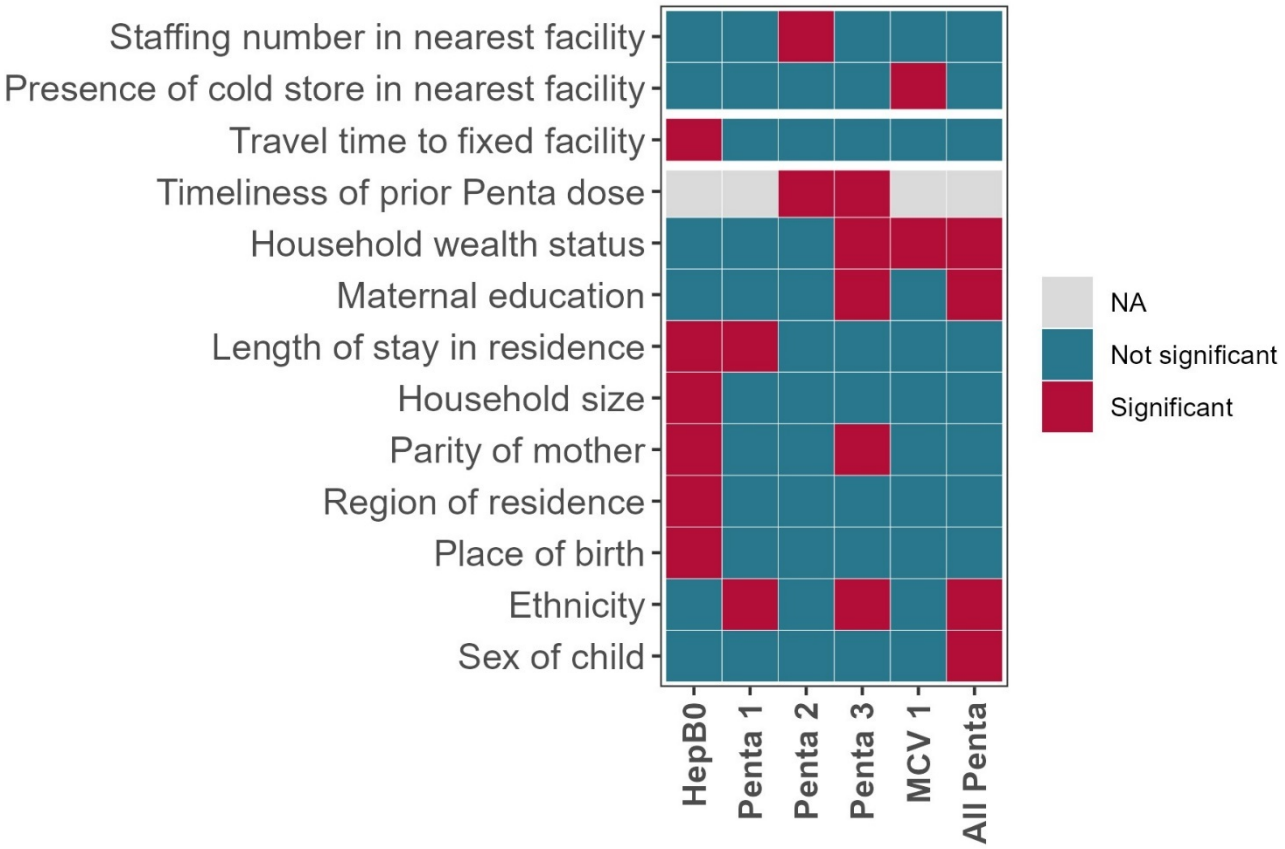


Figure 5: Summary of the estimated relationships of the predictors of timely vaccination in the multivariate analyses. Only variables found to be significant for at least one vaccine are shown**.**

DISCUSSION

Our study examined the factors that influence timely routine childhood vaccination in The Gambia. To achieve this, we utilised two complementary conceptual frameworks that provided a comprehensive theoretical foundation: we examined various quantitative factors that determine the recognition of the need for vaccination from a broader, multi-level perspective (level 1 or demand-side factors). Additionally, we examined the quantitative factors that affect a household or a community's ability to reach immunisation facilities and the ability of these facilities to provide timely vaccinations (level 2 and 3 or supply-side factors). The most common drivers of timely childhood vaccination were demand-side factors such as ethnicity, household wealth status, maternal education, maternal parity, and the duration of the household's residency in its current location. Nonetheless, supply-side factors such as travel time to immunisation facilities, availability of functional vaccine cold storage and staffing numbers in facilities were also significant determinants. Our analysis showed that most demand-side factors were significant for two or more of the vaccines examined. We also found that the determinants of timely vaccination varied across specific vaccines and the timing of doses, which aligns with existing evidence.[29]

For HepB0, a time-sensitive vaccine that must be administered within 24 hours of birth, delivery in a health facility significantly increased timely uptake. Similar findings have been reported in neighbouring Senegal,[46,47] and elsewhere.[29] The increased likelihood of timely HepB0 in facility births can be attributed to immediate access to health professionals who can administer the vaccine within the recommended 24-hour window, unlike in home births. While the 2019-20 GDHS data shows a promising rise in facility deliveries to 84% from 63% in 2013, a concerning 15% of births still occur at home in The Gambia.[33] This translates to missed opportunities for timely HepB0 vaccination. To bridge any remaining gaps and optimise timely HepB0 uptake in The Gambia, further efforts are needed to increase facility deliveries, implement postnatal home visits for timely HepB0 administration, and ensure infants born at home are brought to health facilities promptly, as recommended by the WHO.[48]

Our study also found that shorter travel time to a fixed immunisation facility increased the chances of timely HepB0 vaccination. This is likely because fixed immunisation facilities in The Gambia frequently double as Reproductive and Child Health (RCH) clinics, offering delivery services. As a result, women in close proximity and who potentially give birth at these facilities have access to HepB0 for their newborns. This finding is consistent with previous research in The Gambia[11] and elsewhere,[49,50] that has established a link between geographic proximity to vaccination services and the uptake of routine childhood vaccines. However, our results differed from those reported by Moisi et al in Kenya, who found that travel time to a vaccination clinic was not associated with vaccination coverage or timeliness.[51] This difference in finding could be explained by differences in focus. Our analysis examined travel time to fixed immunisation facilities and its influence on the timeliness of various vaccine doses given throughout infancy, including HepB0, given it's unique time-sensitive nature. Moisi et al.,[51] on the other hand, examined the effect of travel time on vaccines administered later in infancy but did not examine it's affect on HepB0. This further underscore the importance of considering vaccine-specific factors when investigating drivers of timely vaccination.

A key measure of a successful immunisation programme is its ability to consistently reach children on time with multiple doses of the same antigen, like the pentavalent vaccine. Our study revealed that timely administration of subsequent doses of the multi-series pentavalent vaccine is strongly associated with timely receipt of the prior doses. Children who received Penta1 and Penta2 on time were three to five times more likely to receive subsequent doses of Penta2 and Penta3 on time, respectively. This is consistent with previous studies in The Gambia and other contexts that have highlighted the "domino effect," where delays in earlier doses increase the likelihood of delays or non-uptake of later ones.[9,10,52,53] This has important programmatic implications - prioritising interventions that improve the timeliness of the earlier doses of multi-series vaccines could significantly boost overall vaccination timeliness. Based on our findings, programme

managers and service providers should focus their efforts on overcoming any barriers that hinder the timely administration of the first doses in multi-series schedules.

We also found that ethnicity significantly influenced timely pentavalent vaccine uptake. Children from non-Gambian households were substantially less likely to receive Penta1, Penta3, and "All Penta" on time compared to those of specific Gambian ethnic groups. This finding highlights potential barriers to equitable access to vaccination services for non-Gambian children. These barriers could stem from their limited understanding of the immunisation system and other obstacles. Our findings align with past research that has established a connection between ethnic minority status and lower timely vaccination rates.[29,53,54] Since approximately 10% of The Gambia's population are non-Gambians,[33] this finding underscores the urgent need for the EPI programme to prioritise equitable access for ethnic minorities residing in the country. Ensuring everyone, regardless of their background, enjoys the full benefits of vaccination is crucial for achieving improved health outcomes and preventing VPDs, aligning with the "Everyone, Everywhere" vision of the IA2030 agenda.[2]

Measles control serves as a crucial indicator of a strong immunisation system and an important marker of equity within that system. Our study found a significant association between household wealth and timely MCV1 uptake. Children from middle and high-income families were more likely to receive MCV1 on time, aligning with findings from elsewhere.[18,19] While immunisation services in The Gambia are free, indirect costs like transportation and potential income loss from seeking services might deter vaccination, particularly for the poorest households. Moreover, these households often face multi-dimensional poverty, which is a complex problem that goes beyond income.[55] This encompasses various deprivations like limited education, living in urban slums, lack of empowerment in healthcare decisions, and time constraints, all of which can hinder timely vaccination uptake.

Our study identified proximity to an immunisation facility with functional vaccine cold storage as a key factor influencing timely MCV1 uptake. However, limited cold-storage is a persistent challenge in many developing countries. The 2014 WHO multi-dose vial policy, advising on minimizing wastage while ensuring safety, recommends discarding opened vials within six hours unless specific conditions are met.[56] This can lead to "batching" in facilities lacking functional cold-storage, where healthcare workers wait to accumulate enough children before opening a vial to avoid waste. This, unfortunately, can lead to untimely vaccinations, especially for children attending outreach clinics without functional cold-storage facilities. Interestingly, research in The Gambia has shown that over 70% of healthcare workers are willing to open multi-dose vials even if the batching threshold is not met, suggesting potential to optimise vaccination visits and reduce untimely vaccinations.[57] Another promising solution lies in accelerating the implementation of single-use technologies like measles vaccine micro-needle patches.[58] These innovations could reduce

reliance on functional cold-storage and, potentially, improve timely vaccination, particularly in outreach settings.

There are some limitations to the design, dataset, and analytical approach used in this study. Due to the cross-sectional design of our study, we cannot conclude that there is causality between the factors examined and the outcomes observed. Instead, we can only suggest an association, and therefore, the findings should be interpreted with caution. We recognize that we did not consider contextual and qualitative factors such as vaccine hesitancy, beliefs, social norms, rumours, overall trust in government and the immunisation system that can affect a family's decision to vaccinate their children. However, our study concentrated on quantifiable determinants, utilising two robust and complementary conceptual frameworks.

In our analysis of geographic accessibility and facility-level factors that determine timeliness, we assumed that households received vaccination services from the nearest clinic. This might not always be true, as individuals may bypass closer facilities due to perceived service quality issues,[59-61] or service managers may assign communities to specific clinics based on geographic boundaries or operational efficiency, even if they are not the nearest. Additionally, we assumed a constant travel speed in our model and did not account for potential variations in travel time resulting from seasonal changes in travel speed due to poor weather conditions.

To refine future analysis on travel time models and how facility factors impact uptake of timely vaccination, it may be possible to collect information about the specific clinic where services are received using electronic immunisation registers or demographic surveillance systems. It is also important to note that our travel time estimates may have been biased by the random displacement of DHS cluster locations. However, we mitigated this by extracting median travel times within 5 km and 2 km buffer zones for rural and urban clusters, respectively.[39] Additionally, using the complete census of all Gambian immunisation facilities, instead of a limited sample, significantly enhanced the robustness of our travel time models by minimizing potential misclassification errors.[62]

Despite these limitations, our study has several strengths. First, we utilised modelled travel time as a supply-side determinant of timely vaccination, an improvement over reported travel times or distances used in previous studies.[11,19] Second, our two main datasets, the 2019-20 GDHS and the data from the national immunisation facility mapping conducted by The Gambia EPI programme in 2019, were temporally aligned. This improves the quality of our estimates compared to previous studies that have relied on combining facility dataset from databases which may be out of date with population data such as DHS datasets.[63,64] Third, our collaboration with the Gambia EPI improved the facility data with relevant additional variables such as staffing and service scheduling, further enhancing the analysis. Lastly, our study examined broader quantitative factors, diverse vaccines scheduled during different timepoints in infancy, and utilized robust theoretical frameworks to gain a deeper understanding of the complex factors that influence timely childhood vaccination.

In conclusion, our study, guided by robust conceptual frameworks, has provided insight into the key factors that drive timely childhood vaccination in The Gambia. While demand-side factors influencing households' recognition of the need to seek immunisation services were the most prominent determinants, supply-side factors like travel time to facilities, functional cold chain availability, and staffing levels also played a significant role. It's important to note that these determinants varied depending on the specific vaccine and timing of doses. This detailed analysis provides valuable information for immunisation programme managers and service providers. By prioritising interventions and allocating scarce resources based on these identified determinants, they can maximize their impact and ensure children receive timely vaccinations throughout their first year of life.

Authors' contribution

Conceptualization*:** OW conceptualized this study; ***Methodology: OW, with inputs from CEU, UO, WD-G, AS, MS, SF, KM, CG, and BK; ***Project Administration and logistics***: OW; ***Resources***: OW, CEU, KM, BK; ***Data curation***: OW; MS **Analysis:** OW, with support from CEU; **Interpretation of results:** OW, CEU, UO, WD-G, AS, MS, SF, KM, CG, and BK; ***Supervision***: CEU, UO, KM, CG and BK; ***Writing (original draft):*** OW***; Reviewing manuscript***: CEU, UO, WD-G, AS, MS, SF, KM, CG, and BK. All authors approved the final draft of the manuscript and had final responsibility for the decision to submit for publication. OW and CEU had access to all the data in the study.

Ethics approval

The Gambia Government and MRC Unit The Gambia at LSHTM Joint Ethics Committee granted ethical approval for this study (Project ID/Ethics ref: 22786; Date: 16 January, 2021).

Acknowledgements

We would like to express our gratitude to the EPI programme in The Gambia for their close collaboration on this project, for the expert insight and for granting us access to the immunisation facility mapping and census data. We extend our appreciation to Coite Manuel, James McKinnon and colleagues from Crosscut (https://crosscut.io/) for working closely with the Gambia EPI programme during immunisation facility mapping and for providing feedback when we requested information about the facility geolocation process. We thank the DHS programme (https://dhsprogram.com/) for grating us access to the 2019-20 GDHS data, including the cluster GPS coordinates. We are especially thankful to the data management core of the MRC Unit at LSHTM, particularly Mr. Lamin Saidy, for his contribution to the data curation for this study.

Data availability

Data will be made available to anyone for further analyses on reasonable request through the corresponding author, after securing approval from The Gambia Government and MRC Unit The Gambia at LSHTM Joint Ethics Committee.

Patient consent for publication

Not applicable

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Funding

This project is part of the EDCTP2 Programme supported by the European and Developing Countries Clinical Trials Partnership (grant number TMA2019CDF-2734 – TIMELY). The Vaccines and Immunity Theme (OW, UO, and BK) was jointly funded by the UK MRC and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 Programme supported by the EU (MC UP_A900/1122, MC UP A900/115).

Competing interests

The authors declare no conflict of interest. The views expressed in this analysis are those of the authors and do not necessarily reflect those of their parent organisation.

REFERENCES

1. Lai X, Zhang H, Pouwels KB, Patenaude B, Jit M, Fang H. Estimating global and regional between-country inequality in routine childhood vaccine coverage in 195 countries and territories from 2019 to 2021: a longitudinal study. *EClinicalMedicine* 2023; **60**.
2. World Health Organization. Immunization Agenda 2030 - a global strategy to leave no one behind. Geneva, 2021.
3. World Health Organization. Embrace the facts about vaccines, not the myths. 2017. https://www.who.int/news-room/commentaries/detail/embrace-the-facts-about-vaccines-not-the-myths (accessed 17 January 2024).
4. World Health Organization. Harmonizing vaccination coverage measures in household surveys: A primer. Geneva, Switzerland: WHO, 2019.
5. World Health Organization. Measles vaccines: WHO position paper, April 2017– Recommendations. *Vaccine* 2019; **37**(2): 219-22.
6. MacDonald SE, Russell ML, Liu XC, et al. Are we speaking the same language? an argument for the consistent use of terminology and definitions for childhood vaccination indicators. *Hum Vaccin Immunother* 2019; **15**(3): 740-7.
7. Wariri O, Edem B, Nkereuwem E, et al. Tracking coverage, dropout and multidimensional equity gaps in immunisation systems in West Africa, 2000-2017. *BMJ Global Health* 2019; **4**(5).
8. Wariri O, Nkereuwem E, Erondu NA, et al. A scorecard of progress towards measles elimination in 15 west African countries, 2001–19: a retrospective, multicountry analysis of national immunisation coverage and surveillance data. *The Lancet Global Health* 2021; **9**(3): e280-e90.
9. Scott S, Odutola A, Mackenzie G, et al. Coverage and timing of children's vaccination: an evaluation of the expanded programme on immunisation in The Gambia. *PLoS One* 2014; **9**(9): e107280.
10. Odutola A, Afolabi MO, Ogundare EO, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. *BMC health services research* 2015; **15**: 346.
11. Miyahara R, Jasseh M, Gomez P, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. *Vaccine* 2016; **34**(29): 3335-41.
12. Wariri O, Utazi CE, Okomo U, et al. Mapping the timeliness of routine childhood vaccination in The Gambia: A spatial modelling study. *Vaccine* 2023.
13. Wariri O, Utazi CE, Okomo U, et al. Timeliness of routine childhood vaccination among 12-35 months old children in The Gambia: Analysis of national immunisation survey data, 2019-2020. *PLoS One* 2023; **18**(7): e0288741.
14. Phillips DE, Dieleman JL, Lim SS, Shearer J. Determinants of effective vaccine coverage in low and middle-income countries: a systematic review and interpretive synthesis. *BMC Health Services Research* 2017; **17**(1): 681.
15. Bosch-Capblanch X, Banerjee K, Burton A. Unvaccinated children in years of increasing coverage: how many and who are they? Evidence from 96 low-and middle-income countries. *Tropical Medicine & International Health* 2012; **17**(6): 697-710.
16. Santos TM, Cata-Preta BO, Victora CG, Barros AJ. Finding children with high risk of Non-Vaccination in 92 low-and middle-income countries: a decision tree approach. *Vaccines* 2021; **9**(6): 646.

17. Rainey JJ, Watkins M, Ryman TK, Sandhu P, Bo A, Banerjee K. Reasons related to non-vaccination and under-vaccination of children in low and middle income countries: findings from a systematic review of the published literature, 1999–2009. *Vaccine* 2011; **29**(46): 8215-21.

18. Masters NB, Wagner AL, Boulton ML. Vaccination timeliness and delay in low- and middle-income countries: a systematic review of the literature, 2007-2017. *Human vaccines & Immunotherapeutics* 2019; **15**(12): 2790-805.

19. Wariri O, Okomo U, Kwarshak YK, et al. Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps. *PLOS Global Public Health* 2022; **2**(7): e0000325.

20. Utazi CE, Pannell O, Aheto JMK, et al. Assessing the characteristics of un- and under-vaccinated children in low- and middle-income countries: A multi-level cross-sectional study. *PLOS Global Public Health* 2022; **2**(4): e0000244.

21. Choudhary M, Solomon R, Awale J, Dey R. Demand-side determinants of timely vaccination of oral polio vaccine in social mobilization network areas of CORE Group polio project in Uttar Pradesh, India. *BMC infectious diseases* 2018; **18**(1): 222.

22. Gibson DG, Ochieng B, Kagucia EW, et al. Individual level determinants for not receiving immunization, receiving immunization with delay, and being severely underimmunized among rural western Kenyan children. *Vaccine* 2015; **33**(48): 6778-85.

23. Gram L, Soremekun S, Asbroek At, et al. Socio-economic determinants and inequities in coverage and timeliness of early childhood immunisation in rural Ghana. *Tropical Medicine and International Health* 2014; **19**(7): 802-11.

24. Mutua MK, Mohamed SF, Kimani-Murage EW, et al. Complete and on-time routine childhood immunisation: determinants and association with severe morbidity in urban informal settlements, Nairobi, Kenya. *Annals of human biology* 2020; **47**(2): 132-41.

25. Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. *J Epidemiol Community Health* 2012; **66**(7): e14-e.

26. Dejene H, Girma D, Geleta LA, Legesse E. Vaccination timeliness and associated factors among children aged 12-23 months in Debre Libanos district of North Shewa Zone, Oromia Regional State, Ethiopia. *Front Pediatr* 2022; **10**: 867846.

27. Mvula H, Heinsbroek E, Chihana M, et al. Predictors of uptake and timeliness of newly introduced pneumococcal and rotavirus vaccines, and of measles vaccine in rural Malawi: a population cohort study. *PLoS ONE* 2016; **11**(5): e0154997.

28. Périères L, Marcellin F, Lo G, et al. Hepatitis B Vaccination in Senegalese Children: Coverage, Timeliness, and Sociodemographic Determinants of Non-Adherence to Immunisation Schedules (ANRS 12356 AmBASS Survey). *Vaccines (Basel)* 2021; **9**(5).

29. Mansour Z, Said R, Br, et al. Factors affecting age-appropriate timeliness of vaccination coverage among children in Lebanon. *Gates open research* 2018; **2**: 71.

30. Thaddeus S, Maine D. Too far to walk: Maternal mortality in context. *Social Science & Medicine* 1994; **38**(8): 1091-110.

31. Graham B. Population characteristics and geographic coverage of primary care facilities. *BMC Health Services Research* 2018; **18**(1): 398.

32. Wagenaar BH, Gimbel S, Hoek R, et al. Wait and consult times for primary healthcare services in central Mozambique: a time-motion study. *Glob Health Action* 2016; **9**: 31980.

33. Gambia Bureau of Statistics (GBoS) and ICF. The Gambia Demographic and Health Survey 2019-20. Banjul, The Gambia and Rockville, Maryland, USA, 2021.

34. World Health Organization. Vaccination schedule for Gambia. 2023. https://immunizationdata.who.int/pages/schedule-by-country/gmb.html?DISEASECODE=&TARGETPOP_GENERAL= (accessed 29 January 2023).

35. McLafferty SL. GIS and Health Care. *Annual Review of Public Health* 2003; **24**(1): 25-42.

36. Dotse-Gborgbortsi W, Tatem AJ, Matthews Z, Alegana VA, Ofosu A, Wright JA. Quality of maternal healthcare and travel time influence birthing service utilisation in Ghanaian health facilities: a geographical analysis of routine health data. *BMJ Open* 2023; **13**(1): e066792.

37. van Duinen AJ, Adde HA, Fredin O, et al. Travel time and perinatal mortality after emergency caesarean sections: an evaluation of the 2-hour proximity indicator in Sierra Leone. *BMJ Global Health* 2020; **5**(12): e003943.

38. Burgert CR, Colston J, Roy T, Zachary B. Geographic displacement procedure and georeferenced data release policy for the Demographic and Health Surveys: Icf International; 2013.

39. Perez-Heydrich C, Warren JL, Burgert CR, Emch ME. Influence of demographic and health survey point displacements on raster-based analyses. *Spatial demography* 2016; **4**: 135-53.

40. Fox J, Monette G. Generalized Collinearity Diagnostics. *Journal of the American Statistical Association* 1992; **87**(417): 178-83.

41. Snidjers TAB, Bosker RJ. Multilevel analysis. 2nd ed. London: SAGE Publications Ltd; 2012.

42. R Core Team. A Language and Environment for Statistical Computing. Vienna, Austria; 2021.

43. Rue H, Martino S, Lindgren F, Simpson D, Riebler A. R-INLA: Approximate Bayesian inference using Integrated Nested Laplace Approximations. Trondheim Norway; 2013.

44. Adeyinka DA, Muhajarine N, Petrucka P, Isaac EW. Inequities in child survival in Nigerian communities during the Sustainable Development Goal era: insights from analysis of 2016/2017 Multiple Indicator Cluster Survey. *BMC Public Health* 2020; **20**(1): 1613.

45. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd ed. Hoboken, New Jersey: John Wiley & Sons, Inc; 2013.

46. Bassoum O, Ba MF, Sougou NM, Sow A, Seck I. Determinants of timely administration of the birth dose of hepatitis B vaccine in Senegal in 2019: Secondary analysis of the demographic and health survey. *medRxiv* 2023: 2023.12.05.23299481.

47. Bassoum O, Sougou NM, Ba MF, et al. Vaccination against tuberculosis, polio and hepatitis B at birth in Podor health district, Northern Senegal: cross-sectional study of vaccination coverage and its associated factors. *BMC Public Health* 2022; **22**(1): 1-13.

48. World Health Organization. Practices to improve coverage of the hepatitis B birth dose vaccine. Geneva, Switzerland: World Health Organization, 2012.

49. Blanford JI, Kumar S, Luo W, MacEachren AM. It's a long, long walk: accessibility to hospitals, maternity and integrated health centers in Niger. *Int J Health Geogr* 2012; **11**: 24.

50. Metcalf CJ, Tatem A, Bjornstad ON, et al. Transport networks and inequities in vaccination: remoteness shapes measles vaccine coverage and prospects for elimination across Africa. *Epidemiol Infect* 2015; **143**(7): 1457-66.

51. Moïsi JC, Kabuka J, Mitingi D, Levine OS, Scott JA. Spatial and socio-demographic predictors of time-to-immunization in a rural area in Kenya: Is equity attainable? *Vaccine* 2010; **28**(35): 5725-30.

52. Kiely M, Boulianne N, Talbot D, et al. Impact of vaccine delays at the 2, 4, 6 and 12 month visits on incomplete vaccination status by 24 months of age in Quebec, Canada. *BMC Public Health* 2018; **18**(1): 1364.

53. Suffel AM, Walker JL, Williamson E, McDonald HI, Warren-Gash C. Timeliness of childhood vaccination in England: A population-based cohort study. *Vaccine* 2023; **41**(39): 5775-81.

54. Tiley KS, White JM, Andrews N, Ramsay M, Edelstein M. Inequalities in childhood vaccination timing and completion in London. *Vaccine* 2018; **36**(45): 6726-35.

55. Bourguignon F, Chakravarty SR. 337Chapter 18 Multidimensional Poverty Orderings: theory and applications. Arguments for a Better World: Essays in Honor of Amartya Sen: Volume I: Ethics, Welfare, and Measurement: Oxford University Press; 2008. p. 0.

56. World Health Organization. WHO policy statement: multi-dose vial policy (MDVP): handling of multi-dose vaccine vials after opening: World Health Organization, 2014.

57. Usuf E, Mackenzie G, Ceesay L, Sowe D, Kampmann B, Roca A. Vaccine wastage in The Gambia: a prospective observational study. *BMC Public Health* 2018; **18**(1): 864.

58. World Health Organization. Measles and rubella strategic framework 2021–2030. Geneva, Switzerland: World Health Organization, 2020.

59. Amoro VA, Abiiro GA, Alatinga KA. Bypassing primary healthcare facilities for maternal healthcare in North West Ghana: socio-economic correlates and financial implications. *BMC Health Services Research* 2021; **21**(1): 1-14.

60. Makacha L, Makanga PT, Dube YP, et al. Is the closest health facility the one used in pregnancy care-seeking? A cross-sectional comparative analysis of self-reported and modelled geographical access to maternal care in Mozambique, India and Pakistan. *International Journal of Health Geographics* 2020; **19**(1): 1-10.

61. Dotse-Gborgbortsi W, Dwomoh D, Alegana V, Hill A, Tatem AJ, Wright J. The influence of distance and quality on utilisation of birthing services at health facilities in Eastern Region, Ghana. *BMJ Global Health* 2020; **4**(Suppl 5): e002020.

62. Skiles MP, Burgert CR, Curtis SL, Spencer J. Geographically linking population and facility surveys: methodological considerations. *Population Health Metrics* 2013; **11**(1): 14.

63. Ouma PO, Malla L, Wachira BW, et al. Geospatial mapping of timely access to inpatient neonatal care and its relationship to neonatal mortality in Kenya. *PLOS Global Public Health* 2022; **2**(6): e0000216.

64. Joseph NK, Macharia PM, Ouma PO, et al. Spatial access inequities and childhood immunisation uptake in Kenya. *BMC Public Health* 2020; **20**(1): 1407.

PART 3: GENERAL DISCUSSION, CONTRIBUTION OF THE PHD TO LITERATURE, DIRECTION FOR FUTURE RESEARCH AND RECOMMENDATIONS

Chapter 7: General discussion, contribution of the PhD to literature, direction for future research and recommendations

7.1 Overview

When children do not receive vaccinations according to the recommended schedule, they not only miss out on timely protection from preventable diseases when they are most vulnerable, but also heighten their risk of never completing the vaccination course. As new vaccines are continually added to the routine childhood immunisation schedule in many LMICs, programme managers face new challenges in both ensuring uptake of these vaccines and achieving timeliness. Over the next decade, the IA2030 envisions a world where everyone, everywhere fully benefits from vaccines, aiming to introduce 500 new vaccines, achieve 90% coverage and reduce zero-dose children by 50%.[9] While the IA2030[9] and Gavi 5.0 Strategy[29,30] rightfully focus on zero-dose children and improving overall coverage, prioritising vaccination timeliness is equally important. Delayed vaccination, a form of untimely vaccination, often precedes the emergence of zero-dose status,[51] serving as an early warning sign for identifying potential vulnerable subpopulations. The burden and country-level disparities in vaccination timeliness offer a more accurate reflection of effective vaccine doses that are likely to be immunogenic.[26]

The overall aim of this thesis was to investigate the burden and spatial pattern of the various dimension of the timeliness of childhood vaccination in The Gambia and examine the influence of both demand-side and supply-side factors, and the COVID-19 pandemic. To achieve this aim, my thesis had four specific objectives: 1) To systematically review the existing empirical literature on the timeliness of routine childhood vaccination in LMICs, with the aim of identifying the measurement and methodological gaps to inform the design of the PhD research; 2) To describe the burden and the spatial pattern of the various dimensions of the timeliness of childhood vaccination in The Gambia; 3) To determine the impact of the COVID-19 pandemic on the timeliness and coverage of routine childhood vaccination in the Gambia; and, 4) To examine the influence of demand-side factors such as individual and family sociodemographic characteristics, as well as supply-side factors such as geographic accessibility to immunisation clinics and the readiness of these clinics to deliver services on the timeliness of receiving routine childhood vaccination in The Gambia. This final chapter summarises the main findings from the four analytical chapters and discusses their interconnectedness. The subsequent sections discuss the contribution of the PhD research to literature, the implications of the findings for policy and practice, suggest directions for future research and highlight the overarching limitations.

7.2 Summary of findings and their interconnectedness

Identifying the key measurement and methodological gaps in the existing literature on the timeliness of childhood vaccination in LMICs was important to ensure the rigorous design and

implementation of my PhD research. Chapter 3, through a scoping review, revealed that significant variation existed in the definitions of "early," "untimely interval," and "delayed vaccination," even within studies from the same country or focusing on the same vaccine.[78] Furthermore, 'delayed vaccination' was the most commonly studied domain of vaccination timeliness, with many studies operationalising vaccination timeliness as a categorical variable. Demand-side factors, such as individual and household socioeconomic determinants, were most frequently studied, while supply-side determinants, such as factors related to the accessibility of immunisation service points, were understudied.[78]

The significant variation found in the definition of childhood vaccination timeliness demonstrates a lack of agreed-upon standard definition, potentially due to variability in country-level vaccination windows. To bridge this gap and ensure data comparability across antigens and settings, the WHO and national immunisation programmes should develop and implement clear guidelines for measuring vaccination timeliness based on accepted national vaccination windows. Addressing this specific measurement gap for the subsequent objectives of my PhD research, I defined doses received outside the nationally accepted EPI vaccination windows in The Gambia as untimely vaccinations. Specifically, in chapters 4 and 5, 'early vaccination' referred to doses received before the minimum accepted age, while in chapters 4, 5, and 6, 'delayed vaccination' was defined as doses received after the maximum accepted window, as outlined in the national schedule. Although this approach remains specific to The Gambia, it serves several purposes. Firstly, it ensures that future studies on vaccination timeliness in The Gambia, focussing on the same vaccine antigens can be comparable. Secondly, it enables the comparison of my findings with those from other countries sharing similar vaccination windows for specific vaccine antigens. Lastly, even in cases where the vaccination windows differ, the definition, based on doses administered outside the accepted window, facilitates cross-country vaccine-specific comparisons, categorising '*untimeliness*' (early and delayed) as doses outside the window and timely doses as those within the accepted window.

To gain a nuanced understanding of the true burden of untimely routine childhood vaccination, a multidimensional approach is crucial. Findings from the scoping review of existing studies in chapter 3, highlighting a huge focus on 'delayed' vaccination with a categorical proportion-based approach, shaped the design of objectives 2 and 3 (chapters 4 and 5). In examining the burden of vaccination timeliness in The Gambia (chapter 4), I analysed delayed, early, and untimely interval vaccination. Furthermore, to understand the impact of the COVID-19 pandemic on vaccination timeliness (chapter 5), I investigated delayed and early vaccination. In both chapters, I used both categorical and continuous classification methods. This multifaceted approach was essential for this PhD thesis and future studies for several reasons. Relying solely on a categorical, proportion-based metric, while pragmatic, can obscure nuanced interpretations by lumping together a wide

range of untimely vaccinations. Children with longer delays (in days) outside the accepted window potentially have a higher risk of VPD exposure and may be less likely to complete their schedules compared to those with shorter delays.[44,49,50] Additionally, those vaccinated several more days too early, before the minimum accepted age, potentially have less protection due to suboptimal seroconversion due to interference from maternal antibodies.[42]

In chapter 4, the analysis of the burden of the different dimension of vaccination timeliness showed that while overall coverage was above 90% for almost all the vaccine studied, a considerable number of children were vaccinated outside the recommended time-frames. Delayed vaccination was the most common dimension of untimely vaccination in The Gambia, with the highest proportion and longest median number of days children were vaccinated outside the recommended time-frames. Conversely, early vaccination was less common, ranging from 5% to 10%.[79] These multi-dimensional findings facilitated a nuanced interpretation of the quality dimension of the Gambian routine childhood immunisation system performance. However, to effectively design targeted public health interventions, it was imperative to move beyond national and subnational estimates of timeliness. Such aggregate or large areal estimates may conceal epidemiologically relevant local heterogeneities and make it difficult to identify pockets or 'hotspots' of untimely vaccination that could benefit from targeted interventions.

To address the emerging gap subsequent to the initial analysis of the burden of vaccination timeliness in Chapter 4 (i.e., objective 2), I conducted geospatial modelling of the prevalence of delayed vaccination in The Gambia, at 1x1 km² resolution, along with second (district) and third (ward) administrative level maps. This additional analysis focused solely on geospatial mapping of delayed vaccination, excluding other dimensions of timeliness, because the previous analysis highlighted delayed vaccination as the most prevalent in The Gambia. While the scoping review presented in Chapter 3 indicated a growing body of literature examining the timeliness of childhood vaccination in LMICs, no studies, including the three existing Gambian studies, had yet conducted high-resolution maps showing the spatial patterns. In this regard, the spatial mapping of vaccination timeliness in this chapter was both novel and significant, offering EPI programme managers an enhanced understanding of local patterns of delayed childhood vaccination in The Gambia and aiding in the identification of districts where strengthening vaccine delivery systems could yield the greatest impact.

The spatial analysis revealed significant subnational heterogeneity and inequality in delayed vaccination. 'Hotspots' with the highest delays clustered primarily in the eastern region of The Gambia, which is also among the most economically disadvantaged areas. Conversely, coastal and more advantaged districts demonstrated lower prevalence across all vaccines examined. Combining the spatial distribution of delayed vaccination with the absolute number of affected children revealed that districts with both high prevalence and significant absolute numbers of

delayed vaccinations were found in the western (coastal), central, and eastern regions.[80] The analytical approach of combining the spatial distribution of delayed vaccination with the absolute number of affected children is very important. It contextualises the overall analyses, emphasising areas with higher population density, even if the overall delay is lower compared to areas with lower population density but a higher proportion of delays. These population-dense clusters are significant as they can sustain VPD outbreaks such as measles and pertussis in the presence of persistent delays.[54,55,81] In a resource-limited setting like The Gambia, the EPI programme faces two potential public health decisions: to only target interventions in areas with the highest prevalence of delayed vaccination or to target areas with a combination of high prevalence of delays and a high absolute number of affected children. Whichever approach is deemed programmatically or ethically appropriate, the spatial analysis in chapter 4 provides valuable data for evidence-informed implementation.

In Chapter 5 (Objective 3), I examined the impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in The Gambia. There were two main reasons why this analysis was important. Firstly, the pandemic exposed weaknesses in routine childhood vaccination programmes globally, including those in high-income countries with historically high coverage rates. Therefore, it was crucial to gain a detailed understanding of its impact in The Gambia, a low-income country with consistently high routine coverage but a sizeable number of children vaccinated outside the recommended timeframes (as demonstrated in Chapter 4). Secondly, in Chapter 4 (Objective 2), I demonstrated that there was inequality and heterogeneity in the pattern of the timeliness of routine vaccination across different areas in The Gambia. Thus, it was important to investigate whether the COVID-19 pandemic impacted coverage and timeliness differently across regions in the country. By taking this step, the analysis in Chapter 5 builds upon the cross-sectional assessment of vaccination timeliness in Chapter 4 by revealing its temporal pattern and how a major public health crisis may alter the previously observed trends.

Chapter 5 revealed that the COVID-19 pandemic had no significant negative impact on the timeliness (early and delayed vaccination) and coverage of routine childhood vaccinations in The Gambia.[82] Moreover, the pandemic's impact on the coverage and timeliness of vaccination appeared consistent across the two areas studied, despite previously identified differential patterns of vaccination timeliness in Chapter 4. The emphasis in Chapter 5 on both timeliness and coverage, particularly for vaccines administered early in infancy (including the birth dose of hepatitis B vaccine), is important because these metrics are highly sensitive to service disruptions. Therefore, the analysis in this chapter serves as a sensitive indicator of the pandemic's impact on childhood vaccination in The Gambia. This analysis highlights a critical point. While Chapter 4 revealed a substantial number of children vaccinated outside the recommended timeframe, alongside clear heterogeneity in the spatial pattern, this temporal analysis demonstrated that The

Gambia's routine immunisation system effectively absorbed the additional shocks caused by the COVID-19 pandemic. The implications of the findings in Chapter 5 are twofold. Firstly, in the event of future public health crises, The EPI programme can draw upon the same key strategies that ensured the resilience of the routine childhood vaccination system throughout the COVID-19 pandemic. Secondly, the findings offer an opportunity for shared learning, enabling similarly low-income and geographically similar countries facing public emergencies to potentially adopt the key strategies implemented in The Gambia to ensure resilience of their routine vaccination systems.

Chapter 6 (Objective 4) presents a comprehensive analysis of both demand-side and supply-side factors influencing the timeliness of routine childhood vaccination in The Gambia. This study directly addresses a measurement gap identified in the scoping review of Chapter 3 (Objective 1). The review showed that the impact of supply-side factors such as geographic accessibility and readiness of facilities to deliver adequate services on the timeliness of routine childhood vaccinations were understudied in LMICs.[78] To gain a deeper understanding of this complex issue, I analysed diverse vaccines administered at all the timepoints (i.e., at birth, 2, 3, 4, and 9 months) in infancy and utilised two robust conceptual frameworks to guide the analysis. Overall, demand-side factors such as child, maternal and household socioeconomic characteristics influencing the recognition of the need to seek immunisation services were the most prominent determinants of timely vaccination in The Gambia. However, supply-side factors such as travel time to immunisation facilities, availability of functional vaccine cold storage, and staffing numbers in facilities were also significant determinants of timely vaccination. Chapter 6 also revealed that the determinants of timely vaccination varied across specific vaccines and the timing of doses. Based on the empirical evidence from Chapter 6, interventions aimed at improving timeliness must address both demand-side and supply-side factors, rather than prioritising one over the other.

The methodological approach adopted and the findings from Chapter 6 of my thesis are important for several reasons. First, the use of two complementary conceptual frameworks to define and categorise the determinants and to guide the analysis is a novel approach. To my knowledge, no previous study on the determinants of vaccination timeliness has employed this methodological approach. Through this approach, the thesis clearly identified the levels (demand-side or supply-side) at which key determinants lie, thus providing the Gambia EPI programme with evidence to prioritise interventions needed to ensure timely vaccinations in the future. Second, this study is unique because I integrated and analysed two nationally representative and temporally aligned datasets. Other studies are limited by lack of national representativeness or combining datasets from databases that may be out of date with population data such as DHS datasets.[73,83] I collaborated with the national and regional EPI programme managers to verify the national geolocated database of immunisation facilities and updated the dataset with key variables that

were considered very important supply-side determinants. This has further improved the robustness of the dataset and the availability of additional supply-side variables.

Third, the use of the Bayesian multi-level modelling framework ensured greater flexibility compared to the frequentist approach. When fitting multilevel models in a frequentist framework, it is often difficult to characterise variation at the household level when the sample sizes are small, as is often the case in DHS data. In a Bayesian framework, this can be dealt with by placing an appropriate prior distribution on the household-level variation to support its estimation. This additional flexibility to include additional information in the modelling process through placing appropriate prior distributions on the parameters makes the Bayesian paradigm more attractive. Furthermore, elements of survey design, such as clustering and stratification, can be naturally accounted for by using random effects in the Bayesian framework.

Finally, previous research has documented significant misclassification errors and underestimations of service accessibility when geographically linking samples of health facility data with population datasets (e.g., 2019-20 GDHS).[84,85] However, to achieve objective 4 (Chapter 6), I utilised the complete national census of immunisation facilities in The Gambia, linked to the 2019-20 GDHS for the travel time modelling. This comprehensive approach significantly enhances the robustness of the travel time estimates and its potential impact on timely vaccination.[84]

7.3 Contribution of the PhD research to literature

This thesis introduces novel concepts and methodologies for investigating vaccination timeliness. The four analytical chapters (Chapters 3-6) develop or extend novel approaches in data synthesis and integration, methods, and analytical outputs to inform public health decision-making and future research. The contribution to the literature presented in this section is grouped into conceptual, and methodological contributions.

7.3.1 Conceptual contributions

Identifying measurement and methodological gaps

Chapter 3 addresses an important conceptual gap and contributes to the literature on vaccination timeliness by conducting a comprehensive review to identify and document the measurement and methodological gaps within the existing literature. Specifically, the review examines how previous studies have defined and measured timeliness, including cut-off points used for computation, the various dimensions assessed, such as early, delayed, or untimely intervals, and the methods employed for measuring timeliness, both categorical and continuous. It also explores which factors have been considered as drivers of vaccination timeliness.

This work is the most extensive review on the subject to date in LMICs, encompassing four decades of research and analysing 224 studies from 103 countries. While the only previously

existing systematic review on the topic by Masters et al.,[77] offered valuable insights, it had limitations that necessitated a more comprehensive analysis. Firstly, Masters et al.'s review only covered 67 studies published between 2007 and 2017, excluding important work from earlier and later periods. Secondly, it was restricted to three electronic databases and English-language publications, compared to the one in Chapter 3 of this thesis that explored 5 databases and included studies published in English and French Languages. Thirdly, their review did not examine what drivers of timeliness have been previously studied. Lastly, they did not comprehensively explore and document the variety of definitions and cut-off points used for measuring different timeliness dimensions.

By addressing these limitations, the scoping review in Chapter 3 provides a more robust analysis, offering a comprehensive understanding of existing research on vaccination timeliness in LMICs. This work has important implications for future research on vaccination timeliness in LMICs. Consistent definitions and measurement approaches are key for effective communication of research findings, accurate programme evaluation, comparisons across populations and contexts, and robust inference drawn from studies.[25] Understanding the specific dimensions of timeliness studied, the utilised measurement methods (continuous vs. categorical), and the explored drivers of timeliness are all essential for designing future research in this domain. However, the lack of a universally agreed-upon definition of "timeliness" relative to vaccination schedules across different countries presents a challenge. This highlights the need for further efforts to establish standardised measurement approaches in this field, and the conceptual contribution in this regard adequately sets the scene for future efforts.

Examining all dimensions of vaccination timeliness

In Chapter 4, a key conceptual gap is addressed by adopting a multi-dimensional approach to determine the timeliness of routine childhood vaccination. Using nationally representative data, this chapter investigates all dimensions of timeliness, including timely, early, delayed, and untimely interval vaccination. It presents outcomes as both categorical (proportions) and continuous (median days outside recommended windows) variables. This study could potentially be the first in an LMIC context to simultaneously investigate all dimensions of vaccination timeliness and present outcomes using multiple approaches, making a substantial conceptual contribution to the literature.

The adoption of a multi-dimensional approach in Chapter 4 allows for a nuanced interpretation of results, unlike previous studies that primarily focused on delayed vaccination, neglecting other crucial dimensions such as early vaccination and untimely interval vaccination for multi-series vaccines. This one-dimensional focus in previous studies provides insufficient data to gain a holistic understanding of the true burden of vaccination timeliness. Many previous studies have operationalised vaccination timeliness as a categorical variable, predominantly reporting the proportion of children with delayed vaccination. While this approach appears pragmatic, it is

simplistic, lumping together a wide window of untimely vaccinations and preventing a nuanced interpretation of the outcome. Although a few studies have simultaneously explored delayed and early vaccination, they did not examine the dimension 'untimely intervals' between doses for multi-series vaccines. Additionally, they did not present the outcomes as both continuous and categorical variables. Chapter 4 addresses these conceptual limitations.

The multi-dimensional conceptual approach in Chapter 4 enriches the three existing studies[67,69,70] on vaccination timeliness in The Gambia by providing additional evidence on the median number of days children are vaccinated outside recommended timeframes. The conceptual contribution in Chapter 4 allows public health efforts to prioritise not only increasing timely vaccination coverage but also reducing the median days children are vaccinated too early or too late.

7.3.2 Methodological contributions

High-resolution spatial mapping of vaccination timeliness

One of the key methodological contributions of this thesis lies in demonstrating the utility of geospatial modelling techniques for generating high-resolution maps depicting the prevalence of untimely childhood vaccination in The Gambia (Chapter 4). This approach provides timeliness estimates at a resolution of 1km by 1km, along with ward (4th administrative level), district (3rd administrative level), and regional (2nd administrative level) aggregates.

The use of spatial modelling to generate high-resolution maps of health outcomes like childhood vaccination coverage has gained significant traction in recent years. Institutions like the Institute for Health Metrics and Evaluation (IHME) at the University of Washington,[86] USA, and the WorldPop project at the University of Southampton,[87] UK, have spearheaded the development of geostatistical models for this purpose. IHME and WorldPop provide estimates and maps specific to vaccination coverage in LMICs,[32,75,88-90] which are widely utilised by researchers and policymakers globally. The significance of maps in precisely identifying and targeting vulnerable subpopulations is well acknowledged by the WHO IA2030,[9] UNICEF, and Gavi,[91] the Vaccine Alliance.

Despite the significant traction and recognised utility of geospatial modelling approaches in estimating vaccination coverage, to date, no studies have produced high-resolution maps specifically focused on the spatial patterns of the timeliness of routine childhood vaccination. Traditionally, indicators of vaccination timeliness are estimated at the national or regional levels due to survey design limitations or operational constraints inhibiting the collection of location (i.e., longitude and latitude) data needed for spatial modelling. This approach masks epidemiologically important local variations and fails to identify "hotspots" of untimely vaccination. These unidentified pockets of vulnerability hinder efforts to target interventions effectively.

The methodological approach implemented in Chapter 4 represents a novel endeavour, potentially being the first in an LMIC setting to apply geospatial modelling to generate maps of untimely vaccination. By enabling the generation of fine-scale, granular-level estimates, this approach empowers immunisation programme managers to aggregate estimates to administratively relevant units for programmatic decision-making and action. Given the well-developed methodology for spatial modelling and the continued availability of nationally representative vaccination and cluster location data through surveys like DHS and MICS, this approach holds promise for adoption in other settings. However, it's worth noting that minimal data missingness and the availability of vaccination dates and dates of birth are prerequisites for generating timeliness estimates before proceeding to spatial modelling and map creation.

Utilisation of conceptual frameworks to guide analyses

Chapter 6 (Objective 4) of the thesis employs a innovative methodological approach to gain a deeper understanding of the factors influencing childhood vaccination timeliness in The Gambia. This approach leverages two action-oriented conceptual frameworks:

- *The Thaddeus and Maine[92] three delays framework***:** Originally developed to understand the drivers of maternal mortality, this framework explore factors influencing a household's decision to seek services (delay 1), reach health facilities (delay 2), and the ability of the facility to deliver appropriate services (delay 3).
- *The Philips et al.[93] framework for determinants of effective vaccination***:** This framework explore all the dimensions describes by the Thaddeus and Maine framework. Moreover, it categorises the delay 1 factors as demand-side while delay 2 and 3 as supply-side factors.

By applying these frameworks, the thesis comprehensively examines both demand-side factors (influencing household vaccination decisions) and supply-side factors (impacting access to and delivery of vaccination services). This methodological approach facilitated a robust examination of the various factors contributing to untimely vaccination, offering valuable insights for improving vaccination timeliness in The Gambia and beyond.

To achieve objective 4 in Chapter 4 of the thesis, I integrated several datasets. Notably, it demonstrates the possibility of linking DHS survey data with other sources to examine both demand-side and supply-side determinants of timely vaccination. The key datasets integrated include DHS survey data (vaccination data, demand-side factors, and cluster geolocation), national census data of immunisation facilities in The Gambia, gridded population data, and travel time modelling datasets, including digital elevation models, road networks, rivers, lakes, land cover, health facility locations, and DHS cluster locations.

Previous studies in LMICs have primarily focused on demand-side factors as determinants of vaccination timeliness, often overlooking supply-side variables such as geographic accessibility of

immunisation facilities or characteristics affecting a facility's service delivery. Additionally, these studies frequently lacked a guiding framework, leading to an incomplete picture of the key determinants. The methodological approach adopted in Chapter 6 offers distinct advantages. First, it incorporates a wide range of variables in the analysis, enabled by the availability and integration of various temporally aligned data sources. Second, it provides a holistic understanding of the complex factors influencing vaccination service delivery and uptake. Third, the approach delineates where immunisation programme managers should direct their attention, based on factors significantly associated with timely vaccination at either the demand or supply side.

While Chapter 6 considers a broad range of quantitative variables which were informed by the literature, expert opinion, and data availability, future studies could benefit from collecting and including even more comprehensive supply-side variables. This would further strengthen the framework-guided methodological approach for examining drivers of vaccination timeliness as demonstrated in this thesis. Additionally, there is well-documented evidence that qualitative or behavioural issues, such as the behaviour of families, communities and health providers, broadly impact the uptake of vaccination.[94] While this PhD focused on quantitative variables affecting vaccination timeliness, there is a clear need for future qualitative research to understand the specific impact of behavioural issues on vaccination timeliness. Outputs from such qualitative studies, combined with the quantitative evidence from this PhD, could lead to the development of more robust and targeted public health interventions to improve timeliness.

7.4 Implications for policy and practice

In the discussion sections of each analytical chapter (Chapters 3, 4, 5 and 6) of this thesis, I highlighted the implications of specific findings for policy and practice. In this section of the final chapter, I focus on the broader implications of my PhD research for various stakeholders. I explore these implications across four key areas, highlighting the significance of the findings for vaccine and vaccination policy, with a specific emphasis on Global Policy, the Gambian Government, Programme Managers overseeing the Gambian immunisation system, and local communities.

7.4.1 Implications for Global Policy

The findings reported in Chapter 3 (objective 1) underscore the importance of collaboration between the WHO and national immunisation programmes to address the variations in defining and measuring the various dimensions of vaccination timeliness. To ensure data comparability, clear guidelines for measuring all aspects of timeliness should be developed and implemented. These guidelines should be based on accepted national vaccination windows and not individual researcher or country preference.[26,95] By establishing standardised age cut-off for assessing timeliness, the WHO can empower countries to accurately monitor and report on this critical aspect of their vaccination programmes. This approach would allow countries to detect problems with

vaccine delivery and coverage at an early stage, across different populations. Early detection of untimely vaccination is essential to achieve effective overall coverage and reduce the risk of undetected, yet accumulating risk of VPD outbreaks.[13,45,53,54] Furthermore, measuring timeliness correctly can serve as an early warning system for gaps in vaccine coverage and herd immunity. This is because untimely vaccination, particularly delays, often precedes a decline in vaccination uptake or an increase in zero-dose cases. Ultimately, it is important to ensure that vaccination timeliness, a key metric of immunisation system performance, is included in future vaccine-specific global health agendas, such as the IA2030.

7.4.2 Implications for the Gambian Government

Chapter 6 (Objective 4) highlights the role of demand-side factors, such as maternal education, household wealth status, ethnicity, and place of birth, as key determinants of timely vaccination. While immunisation programme managers may not have direct control over these demand-side factors, they fall within the broader domain of government intervention. Urgent government investment, prioritisation, and targeted policies are required to address these social determinants of health. Research indicates a clear link between government investment in human capital development, reduced inequalities, and improved child health outcomes.[96,97] Disadvantaged populations, in particular, are consistently at the highest risk of poor health outcomes, including untimely vaccination. In this regard, the evidence from this thesis can be used to reduce inequities in the spatial pattern of untimely vaccination in The Gambia.

Moreover, Chapter 6 also underscores the significance of supply-side factors, such as travel time to fixed immunisation clinics. Improving this aspect requires substantial government investment to provide functional fixed immunisation clinics that are easily accessible to the majority of the population, facilitating regular and timely access to vaccination services. Giving priority to the development of social infrastructure, such as building accessible roads across the country and increasing the availability of functional fixed immunisation facilities, can significantly enhance access to immunisation services, particularly in underserved areas. However, it is crucial to conduct cost-benefit and cost-effectiveness analyses to determine the costs to the health system and the return on investment for the additional government funding needed to improve vaccination timeliness and overall coverage. Given scarce resources and limited fiscal space, evidence from such economic analyses will be key to determining what combination of demand- or supply-side interventions should be prioritised to enhance the EPI's delivery of childhood vaccines within recommended timeframes in The Gambia.

7.4.3 Implications for immunisation programme managers in The Gambia

The high prevalence of delayed vaccinations identified in Chapter 4 (Objective 2) highlight the need for urgent action by EPI programme managers. Strategies to reduce delays should focus on

strengthening outreach sites to deliver more frequent services, increase the overall number of immunisation facilities to improve overall clinic accessibility and fostering stronger community engagement. Chapter 6 (Objective 4) highlights the crucial role of staffing numbers in immunisation facilities as a key driver of vaccination timeliness. The capacity issues related to staffing must be prioritised to ensure effective and timely delivery of immunisation services. Inadequate staffing can lead to long queues at immunisation clinics, which have been previously reported by women in The Gambia as a deterrent from attending immunisation clinics.[98]

Of particular concern is the finding in Chapter 4 that the birth-dose of Hepatitis B (HepB0) vaccine had the highest delays (more than 90%) and median delay (in days). This has significant implications for immunisation programme planning and policy. Chronic Hepatitis B virus (HBV) infection can lead to serious complications like liver cirrhosis and cancer. The Gambia faces a high burden of HBV, with 15-20% of the population chronically infected,[99] making mother-to-child transmission during birth and breastfeeding common. The Gambia requires immediate measures to improve the timeliness of HepB0 delivery and uptake, in order to address the current situation. Chapter 6 (Objective 4) identified key drivers for timely HepB0 vaccination, including being born in a health facility and living close to a fixed immunisation clinic. While these factors may not be directly controllable by the EPI, collaboration with health facility management and the Ministry of Health can help align priorities.

The EPI programme should prioritise equitable access to services nationwide by addressing potential barriers related to ethnicity. This is especially important in areas identified as "hotspots" for untimely vaccinations through the spatial mapping in Chapter 4 (Objective 2). Furthermore, the consistent finding of ethnicity (alongside household wealth) being the most common factor associated with timely vaccination across the vaccines studied suggests that further investigation of potential ethno-cultural differences in timely access to immunisation is warranted. This could inform the development of targeted interventions to address these disparities and improve equitable and timely access to immunisation services for all populations in The Gambia.

7.4.4 Implications for household and communities

Families and households play a pivotal role in ensuring the timely vaccination of children within accepted timeframes. This responsibility is underscored by the significant associations found between household characteristics—such as maternal education, parity of the mother, household size, and ethnicity—and timely vaccination, as revealed in Chapter 6. Previous research conducted in The Gambia has also indicated prevalent patterns of under-vaccination among children from poorer households and recent non-Gambian immigrants, who often face social exclusion at infant welfare clinics.[98] My findings, along with evidence from prior research, emphasise the need for targeted health education and awareness campaigns aimed at these specific subpopulations. Such

campaigns must stress the importance of timely vaccination in preventing diseases and offer culturally sensitive resources to enhance comprehension of the key messages.

It is important to note that there is a prevailing acceptance and trust in immunisation services across The Gambia. Previous studies have demonstrated that instances of non-uptake likely stem from logistical challenges, such as the inability to transport children to immunisation clinics or from mothers mistakenly believing their children do not require the next dose rather than from resistance to immunisation per se.[100] This underscores the importance of education and awareness campaigns. By empowering families to prioritise age-appropriate vaccination, particularly in communities identified as 'hotspots', households can contribute significantly to enhancing overall timely vaccination rates and reducing the risk of disease transmission.

7.5 Direction for future research

Throughout the four analytical chapters, several priorities for future research on the timeliness of routine childhood vaccinations were identified and discussed. In this section, I highlight the specific direction that future research on the timeliness of routine childhood vaccinations can take, in order to effectively integrate this emerging area of research with the broader field of vaccine epidemiology. The following sections present these priority areas in some detail.

7.5.1 Examining the direct relationship between untimely vaccination, population immunity, and susceptibility to outbreaks

A fundamental question arising from this PhD research is: "*To what extent does the timeliness of vaccination impact population-level immunity, and how does it influence the potential for outbreaks?*" At the time of finalising this PhD, The Gambia is experiencing an uptick in measles cases, even in areas with optimal aggregate measles vaccination coverage rates. Furthermore, a quarter of the confirmed cases are among children who have already been vaccinated. It is imperative to investigate the degree to which untimely (early and delayed) uptake of measles-containing vaccines, in addition to postponed measles campaigns and stagnating measles-containing vaccine coverage, contribute to measles population immunity and the accumulation of susceptible sub-populations. However, the relationship between the clustering of children with untimely measles vaccination, suboptimal measles population immunity, and risk of measles outbreaks in the same spatial location is largely understudied in LMICs context.

Defining the landscape of population immunity and susceptibility to outbreaks is a key challenge in infectious disease research.[101,102] Previous studies have primarily relied on indirect measures, such as crude vaccination coverage and outbreak surveillance data, to estimate these factors.[102,103] However, the patterns of population immunity predicted from indirect measures may be misleading especially in settings with non-sensitive surveillance systems.[102,104] Serological surveys offer a

more direct approach to assess population immunity, identify potential links to untimely vaccination, and predict outbreak susceptibility.[105] Despite their power, serosurveys often remain underexploited due to cost and logistical complexities.[102]

Recently, I was awarded a 5-year K43 Emerging Global Leaders Award from the US National Institutes of Health (NIH). As the Principal Investigator of this 5-year Award, I will be examining the potential link between untimely measles vaccination, suboptimal herd immunity, and measles outbreak risks.[106] Therefore, the key question arising from the PhD about any potential link between untimely vaccination and population immunity will be answered. Over the next five years, I will utilise longitudinal seroepidemiologic and vaccination data to model measles population immunity, examine spatiotemporal relationships between clusters of children with untimely measles vaccination, and predict outbreak susceptibility profiles in The Gambia.

7.5.2 Refining travel time estimates and their impact on vaccination timeliness

The current approach to estimating travel time, both in this PhD research and in other existing studies, faces key limitations due to data availability issues. Present methodologies rely on proxy variables, such as travel time to the 'nearest clinics', rather than the actual clinic used, as linking study populations to specific vaccination locations can be challenging. Additionally, existing studies typically neglect actual travel scenarios and seasonal variations in travel times. Furthermore, they have primarily focused on accessibility between households and clinics, neglecting to explore how accessibility between fixed vaccination clinics and outreach vaccination posts influences vaccination delivery by service providers.

In The Gambia, childhood vaccination is conducted through a distinctive system utilising fixed vaccination clinics and outreach posts managed by service providers from these fixed clinics. These providers may encounter numerous challenges when travelling from supervising fixed vaccination clinics to remote or isolated outreach vaccination posts. Future research should prioritise linking households to the actual clinics where children receive vaccinations. This will involve collecting detailed data on travel scenarios, leading to more accurate, closer-to-reality travel time estimates. Such an approach will provide a more nuanced understanding of how seasonal variations, such as changes in weather, impact accessibility and subsequently influence untimely vaccinations. Moreover, future studies should investigate how the ease or difficulty of service providers' travels from fixed vaccination clinics to outreach vaccination posts—a crucial supply-side variable—affects the timely delivery of routine childhood vaccination.

7.5.3 Real-time vaccination timeliness dashboard and time-trend analysis

One promising avenue for future research lies in the development of a real-time immunisation dashboard specifically focused on vaccination timeliness. The timeliness of vaccine delivery serves as a valuable quality indicator for immunisation programmes, potentially offering an early warning

system for areas experiencing challenges. Delayed vaccinations can disrupt the recommended schedule and potentially lead to missed doses, while excessively early vaccination may signal areas where the vaccination system is struggling to deliver vaccines effectively. However, traditional research data, including findings from this PhD often lags behind real-time activities, limiting its immediate translation for public health or usefulness for programme managers.

To bridge this gap and ensure that research effectively informs practice, future research should explore the development and implementation of real-time vaccination timeliness dashboards. Such a system could leverage electronic immunisation registers, geolocation data, coupled with the modelling and analytical approach developed during this PhD. This dashboard would provide vaccine-specific timeliness estimates, including early, delayed, untimely interval, and timely vaccinations, as well as spatial patterns of timeliness. Although this concept shows promise, translational research is necessary to assess its feasibility and overall utility in LMIC settings. Ultimately, the creation of such a dashboard has the potential to enable immunisation programmes to rapidly identify locations experiencing un- and under-vaccination much earlier, thereby contributing to the goals of IA2030.

Although this PhD analysed the impact of additional 'shocks' to the EPI system due to the COVID-19 pandemic, the data underlying the analysis were not nationally representative. To better understand the spatiotemporal impact of future 'shocks' or public health crises on vaccination, more robust methods, data sources, and alternative analytical approaches might be needed. Demographic and health surveillance systems could provide granular and temporal data for such analysis; however, they are not nationally representative in most countries where they exist. There is a clear need to expand their coverage, but this comes with significant cost implications, as most HDSSs are neither funded nor led by governments. Future spatiotemporal analyses of vaccination timeliness could also benefit from combining data from consecutive DHS and MICS surveys, given their methodological similarities and the fact that they are often conducted less than two years apart. Another source of data for such time-trend analysis are electronic immunisation registers, which have been implemented in many LMIC settings. However, these registers are limited because they only include children who have interacted with the immunisation system.

7.5.4 Addressing missing vaccination dates in future timeliness analysis

Accurate dates of birth and vaccination are crucial for computing vaccination timeliness, and a high proportion of children with complete data is essential for representative outcomes.[95] In cases where vaccination dates are unavailable, this data is considered "censored." Children who have not been vaccinated at the time of data collection, and thus have unavailable vaccination dates, are considered right-censored. Meanwhile, children who have already been vaccinated but lack vaccination date records are considered left-censored. Unfortunately, the majority of studies

included in the scoping review in Chapter 3 (Objective 1) did not account for any form of censoring and instead excluded the data of such children,[78] potentially underpowering these studies to generate representative timeliness outcomes.

Left-censored data is particularly common in LMICs due to low card retention, and vaccination data often rely on maternal recall. However, in my timeliness analyses in Chapters 4 and 5 of this PhD, this was not the case as over 90% of children had complete vaccination dates. Accounting for censored data enhances the robustness of timeliness estimates by enabling the inclusion of more observations that might otherwise be excluded. To conduct timeliness analyses in settings where card retention is low, reliance on parental recall is common, or where left-censored vaccination data is prevalent, it is essential to develop, validate, and deploy methodologies that can impute or predict the dates of vaccination. These imputation or prediction techniques could utilise machine learning approaches that leverage pre-specified characteristics, such as the age at vaccination of children in similar age cohort as the index child or those residing in the same geographic location—a key factor driving spatial autocorrelation.[107] Although such prediction approaches might be time-consuming or require modelling expertise, they are crucial to ensuring that timeliness analyses are appropriately powered to generate accurate outcomes. Ultimately, there is a need for significant government investment to expand and improve data infrastructures, such as electronic immunisation registers in LMIC settings, thereby enhancing the availability of precise vaccination dates.

7.5.5 Methodological approaches to model all outputs as continuous variables

Communities where children experience longer delays in receiving vaccinations potentially face an increased risk of exposure to VPDs and potential outbreaks compared to communities with shorter vaccination delays. However, the current approaches only allow for the generation of untimeliness outcomes as continuous variables when determining the burden of delays (e.g., mean/median delays in paper 1, Chapter 4), but not for spatial modelling or determinants, which are categorical or binary. Therefore, there is a need to develop methodologies for more complex analyses that go beyond the current categorical outcomes. For example, geospatial modelling of vaccination timeliness could produce continuous outcomes rather than the current binary outcomes. Such complex analysis could lead to the creation of maps showing locations with the mean or median number of days children are delayed compared to other areas. This approach offers the advantage of enabling EPI programmes to prioritise the most vulnerable communities where delays are longer, rather than relying on the current binary outcomes of 'delayed' and 'not delayed.'

With the current methodologies of geospatial modelling, when the outcome is continuous, the binomial likelihood is no longer suitable. A potential methodological approach involves changing the binomial likelihood to a probability distribution defined on the positive real line, such as a half-normal distribution or a gamma distribution. Additionally, the log-transformed version of the

outcome could be modelled using a normal distribution. Other components included in the current model framework, such as covariates and spatial random effects, can still be used when the distribution of the outcome changes, although the functional form of the covariates may be different. Whatever complex approaches are developed, these need to be calibrated and validated to ensure their robustness, similar to the current approach of geospatial modelling of binary outcomes.

7.5.6 Methods to evaluate potential interventions to improve timeliness

Various interventions have been implemented to improve vaccination coverage in LMIC settings. These include patient phone reminders, digital registers, household financial incentives, health education, home visits, engagement of community leaders, supportive supervision, payment for performance and logistic support to health facilities.[108] Additionally, the use of novel interventions, such as drones (unmanned aerial vehicles) for delivering vaccines to hard-to-reach communities, is gaining momentum. While these interventions have been broadly targeted at improving vaccination uptake, they may also positively impact vaccination timeliness. However, evaluating these interventions specifically in the context of their effectiveness in improving vaccination timeliness is crucial. Future research could employ methods such as cluster randomised trials or pragmatic approaches like before-and-after studies to assess these interventions with the specific goal of enhancing vaccination timeliness.

7.6 Limitations

Limitations specific to each individual study were extensively discussed in the relevant research papers from Chapter 3 to Chapter 6 of this thesis. In this section, I provide a summary of the key limitations discussed in the research papers in their respective chapters (Table 1). Subsequently, I address the more general limitations of the PhD research and those that were not discussed in the corresponding chapters.

Table 1: Summary of the key limitations already presented in the analytical chapters

Chapter (Paper)	**Limitations**
Chapter 3	1. The review included only studies published in English and French. Thus, may have omitted a small number of studies published in other languages. 2. The review did not include grey literature, such as official government reports on vaccination timeliness. 3. Some studies might have been published since the scoping review was completed on July 1, 2021, as this study is not a 'living review.' However, I do not expect them to significantly alter the conclusions drawn from the scoping review, which was based on 224 published articles spanning 1978–2021.

	4. The scoping review did not include studies on vaccinations given outside the routine childhood EPI schedule, such as those administered during adolescence or adulthood, including maternal vaccinations. 5. Although appraising study quality or design is not the primary focus of scoping reviews, there was substantial variability in the quality and design of the included studies, which potentially explains the observed measurement and methodological gaps.
Chapter 4 (Paper 1)	1. The use of DHS data for the analysis of vaccination timeliness presents limitations inherent to the nature of survey data. Specifically, the unavailability of valid birth dates and vaccination dates for a substantial number of children in some LMIC settings can introduce biases and limit the generalizability of timeliness estimates in such contexts. 2. Cross-sectional surveys like DHS provide a snapshot of the population at a specific point in time. Since the data is typically collected every five years and focuses on children who were vaccinated 12–35 months before the survey was conducted, the findings reported do not reflect the most recent vaccination status.
Chapter 4 (Paper 2)	1. The sampling frames used in the 2019–20 GDHS may have missed hard-to-reach or disadvantaged populations, potentially leading to an under- or over-estimation of the prevalence of delayed vaccination in certain areas. 2. To ensure respondent confidentiality, the DHS randomly displaced the geographical coordinates at the cluster level. Although we created buffers around the coordinates in rural and urban locations in line with previous approaches, there might have been some residual influence on the modelled estimates, especially at a more granular level. 3. The 2019–20 GDHS sample was designed to be representative at the national and regional levels, considering urban/rural stratification, not at the lower district or ward level where our results were presented. However, the Bayesian spatial modelling approach utilized in this analysis has been well validated and is known to provide robust estimates at finer scales.
Chapter 5	The underlying data was based on HDSS surveillance. HDSS communities are observed longitudinally, and households participate in multiple studies where they often receive interventions, including vaccinations. This might make them unrepresentative of the general population. Additionally, some individuals or households within the HDSS communities might modify their behaviour because they are aware they are part of a surveillance system—*the Hawthorne effect.*
Chapter 6	1. Due to the cross-sectional design of our study, we cannot establish causality between the significant determinants and the outcomes observed. 2. The study did not consider contextual and qualitative factors such as vaccine hesitancy, beliefs, social norms, rumours, and overall trust in the government and immunization system that can affect a family's decision

	to vaccinate their children. Instead, the study focused on quantitative and measurable determinants. 3. In the analysis of geographic accessibility and facility-level factors determining timeliness, we assumed that households received vaccination services from the nearest clinic. This might not always be true, as individuals may bypass closer facilities due to perceived service quality issues, or service managers may assign communities to specific clinics based on geographic boundaries or operational efficiency. 4. In the analysis of travel time, we assumed a constant travel speed in the model and did not account for potential variations in travel time due to seasonal changes and poor weather conditions. 5. The travel time estimates may have been biased by the random displacement of DHS cluster locations. However, we mitigated this by extracting median travel times within 5 km and 2 km buffer zones for rural and urban clusters, respectively.

The more general limitations of the PhD research that have not been discussed so far in the corresponding research papers presented in the analytical chapters are presented below.

7.6.1 Generalisability of the findings

In Chapter 5, I observed no significant negative impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccination in The Gambia. Instead, there was an improvement in coverage and timeliness in the second year of the pandemic. However, it is essential to acknowledge that the analyses might be constrained by the fact that the data underlying the findings originated from two large HDSSs located in the eastern and central parts of The Gambia. These areas are less urban and less populated compared to the more urban and densely populated western part of the country, which constitutes about 60% of the national population.[109] Additionally, the western part, particularly the greater Banjul Area, experienced the majority of COVID-19 cases during the peaks of the pandemic,[109] potentially resulting in more disruptions to vaccination service delivery.

Given these factors, the generalisability of the findings in Chapter 5 to the entire population may be limited. Nevertheless, the findings in Chapter 5 hold validity due to several factors. The data was based on robust population surveillance collected through quarterly HDSS censuses. This data encompasses nearly 60,000 children in over 9,000 households across more than 300 communities, spanning January 2017 to December 2021. While the HDSS offers the most robust longitudinal cohort data in The Gambia, there is a need to expand its coverage to include communities in the western and more urban parts of the country.

While the key findings from Chapters 3, 4, and 6 may be generalisable to the Gambian population due to the nationally representative datasets used, generalisability to other settings might be

limited. This limitation stems from specific contextual factors unique to The Gambia, such as social norms, traditional beliefs, and the level of trust in constituted authorities, which influence the uptake of vaccination services.[98,100] Moreover, The Gambia's relatively small population and historical success in the immunisation system further shape the delivery of services. Consequently, these contextual factors may hinder the direct generalisability of the findings from this PhD, including the burden, spatial pattern, and determinants of routine childhood vaccination to high-income countries or every LMIC context.

Despite limited generalisability to every setting, the findings from this PhD can guide immunisation programme managers in certain contexts, particularly in sub-Saharan Africa with similar geography, immunisation system and small population sizes, such as Cape Verde, which also shares a regional context with The Gambia. Even with differences in population size, the findings may also be applicable to sub-Saharan African countries like Senegal, Ghana and Malawi, whose immunisation systems are 'maturing' or high performing like The Gambia. While the generalisability of the findings might be limited in broader international settings, the analytical approach developed during this PhD can be adapted and scaled to conduct similar timeliness analyses elsewhere. This is particularly relevant given the growing availability of nationally representative surveys like the DHS and MICS in many LMIC settings in Africa, Southeast Asia and Latin America.

7.6.2 Time-lagged findings

One major limitation of this PhD study is that the findings are based on time-lagged data, which may not accurately represent the current situation of the burden, spatial pattern and determinants of the timeliness of childhood vaccination in The Gambia. While the analytical chapters offer valuable insights, the datasets used were several months old at the time of publication, and dissemination of findings. Given the time-sensitive nature of routine childhood vaccination, real-time data is necessary to inform strategies for improving vaccination timeliness. Unfortunately, obtaining sufficiently timely data, to make data-informed decision is a significant challenge in many sub-Saharan African and LMIC settings due to poor data infrastructure.[110-112] This limitation is not unique to this PhD study but is present in majority of the empirical studies on the timeliness of childhood vaccination reviewed in Chapter 3.

To overcome this challenge, substantial government investment and locally tailored approaches are necessary to generate real-time, high-quality, population-based vaccination data. Monitoring real-time and temporal trends in vaccination timeliness is critical to evaluating the effectiveness of targeted interventions over time. Fortunately, my recently awarded NIH K43 Award will allow me to address this gap. Using real-time longitudinal cohort data from HDSS and electronic immunisation registers, I will investigate the spatiotemporal patterns of untimely measles vaccination in The Gambia.

7.6.3 Individual facility characteristics versus weighted composite variable

In Chapter 6, I investigated the supply-side determinants of timely vaccination by analysing individual characteristics of immunisation facilities, such as type, ownership of functional vaccine cold storage, number of health workers delivering vaccines, population of children within the catchment area, and frequency of facility operation per month. However, the reliance on individual facility characteristics, rather than a combined effect of these characteristics, represents a potential limitation of the study's findings.

A more informative approach might have been to create a weighted composite variable representing an "ideal immunisation facility" that incorporates all the relevant characteristics. This would enable the evaluation of how facilities that come closer to this 'ideal' determine timely vaccination. However, constructing such an "ideal facility" composite variable requires further refinement and weighting, considering the relative importance of each domain of the vaccination facility characteristics. Determining the relative importance of staffing levels compared to vaccine cold storage ownership, or the relative importance of catchment area population compared to staffing levels, poses challenges. Additionally, assessing the relative importance of a facility's status as a fixed site versus an outreach site delivering services weekly presents further complexities. Unfortunately, there's limited empirical evidence on how much weight to give factors like staffing levels compared to cold storage ownership, or catchment population compared to staffing. Without clear weighting, developing a robust composite variable was not feasible for the study in Chapter 6. Therefore, I opted for analysing the influence of each individual characteristic on timely vaccination.

7.7 Recommendations

This PhD research examined timeliness of routine childhood vaccination using robust methodologies to understand its burden, spatial patterns, determinants, and how COVID-19 impacted the burden in The Gambia. The overall design and analytical approach were informed by a scoping review of existing literature on vaccination timeliness from LMICs spanning over four decades. The research was conducted in The Gambia, which has unique circumstances as a relatively small country in terms of both geography and population size. Additionally, the country has consistently maintained high childhood immunisation coverage rates, similar to those achieved in many resource-rich countries for almost two decades before the COVID-19 pandemic. In this sense, The Gambia immunisation system can be considered as 'maturing'.

Based on the findings from this PhD research, I offer the following specific recommendations to guide national EPI programmes and global immunisation policymakers;

1. Global immunisation policymakers, including the WHO, need to prioritise vaccination timeliness as a key measure of immunisation program performance. In the context of

LMICs, this prioritisation should focus on countries with 'maturing' immunisation systems, where routine coverage rates are high or approaching global targets. This emphasis is important because, as demonstrated in this PhD research, high overall coverage in a high-performing programme like The Gambia did not necessarily translate to high timely vaccination, which is also essential for preventing VPDs such as hepatitis B and measles. In countries where coverage rates are still suboptimal, the strategy should remain focused on increasing overall coverage without the additional burden of ensuring timeliness.

2. Based on the dichotomy highlighted above, expert opinion is required to define the specific level of vaccination coverage that must be achieved before countries can start prioritising vaccination timeliness as a key performance indicator. The WHO Strategic Advisory Group of Experts (SAGE) on Immunisation, as well as the Regional and National Immunisation Technical Advisory Groups (RTAGs and NITAGs), could provide evidence-based recommendations to guide this process.
3. Irrespective of the coverage level or 'maturity' of a country's EPI programme, the timeliness of the HepB0 must be prioritised globally. As recommended by the WHO, to reduce mother-to-child transmission (MTCT) of hepatitis B, all children should receive HepB0 within the first 24 hours of birth, especially in hepatitis B endemic settings. As shown in this PhD, even in The Gambia, where overall coverage of HepB0 was above 95%, only about 1 in 10 infants received the vaccine within the recommended 24 hours, despite the endemic nature of the virus. Evidence indicates that scaling up timely HepB0 vaccination (i.e., within 24 hours of birth) to 90% of infants in LMICs by 2030 could prevent 710,000 deaths in the 2020 to 2030 birth cohorts compared to the current status quo.[113] The greatest benefits would be in Africa, with the potential to eliminate MTCT of hepatitis B by 2030 in the Americas and by 2059 in Africa.
4. There is a need for an agreed-upon definition of all dimensions of vaccination timeliness. While the recommended timing for administering certain vaccines may vary across countries, I recommend that the definition of timely vaccination should be based on doses administered within the recommended window in each country, rather than using an arbitrary cutoff. This pragmatic approach will ensure that data can be compared across countries and regions. Additionally, many LMICs currently follow the WHO-recommended schedule of '6 weeks, 10 weeks, 14 weeks, and 9 months.', further strengthening this recommendation.
5. When researching vaccination timeliness, the results should be reported using a multi-modal approach, combining continuous outcomes (e.g., the mean or median number of days vaccines were received too early or too late) with categorical outcomes (e.g., the proportion of the target population vaccinated too early or too late). This approach allows for a nuanced interpretation of the data, as locations with the highest proportion of delays

may not necessarily be the same as those where children are vaccinated significantly outside the accepted windows. Both scenarios indicate different levels of risk and programme performance.

6. Future research should incorporate fine-scale spatial analysis, as demonstrated in this PhD, in addition to aggregate-level or large-area estimates, which often mask heterogeneities or inequalities in vaccination timeliness. This is particularly important at sub-regional or continent-wide levels to understand intra- and inter-country inequities in vaccination timeliness, especially for vaccines against highly infectious VPDs like measles. Fine-scale spatial analysis of vaccination timeliness, alongside established spatial analyses of overall coverage and zero-dose prevalence, will better guide targeted interventions.
7. In scenarios where data missingness is high, conducting timeliness analysis might be inappropriate, and it is crucial to determine the acceptable level of missingness for such analysis. A power analysis should be conducted to ensure that the available data with complete dates of birth and vaccination are adequately powered and representative of the study population. Additionally, methodological approaches should be developed to predict potential vaccination dates if the rate of missing birth and vaccination dates is high, before proceeding with the timeliness analysis.
8. Government investment is needed to improve data quality and data systems in LMICs to ensure the availability of precise information on dates of birth and vaccination, which are essential for conducting timeliness analysis. These efforts should include training and retraining of immunisation providers to ensure accurate recording of vaccination dates on vaccination cards. Additionally, more innovative methods for storing hand-held immunisation information or cards should be developed. This could be achieved through mobile applications, especially as the use of smartphones and the availability of high-speed, affordable internet continue to grow in many LMIC settings.
9. There is limited direct evidence linking untimely vaccination to VPD outbreaks or increased disease burden, although some modelling evidence exists. Therefore, there is a need to generate real-world data to understand the impact and relationship between untimely vaccination and VPD outbreaks or increased disease burden.
10. To improve timely vaccination rates, qualitative research is also needed to explore how parental attitudes, family dynamics, and community factors influence vaccination decisions.

7.8 Concluding remarks

As the deadline for achieving the goals set out in the IA2030 approaches, with just six years left in the 'Decade of Vaccines,' the momentum towards achieving these goals is palpable. Despite the challenges posed by COVID-19, significant progress is being made, especially in the context of the 'Big Catch-Up.' New routine vaccines are being introduced in many countries, and overall coverage

is improving in many underperforming settings. Additionally, the efforts to reach zero-dose children, particularly in high-priority areas, have been remarkable.

However, amidst these achievements and new priorities, there is a significant risk of halting or even reversing hard-won gains, particularly in high-performing or ‘maturing’ immunisation systems like The Gambia. This could happen if we fail to prioritise and measure more sensitive domains of immunisation system performance, such as vaccination timeliness. While enhancing overall vaccination coverage rates and reaching zero-dose children are crucial, focusing on these alone may obscure the importance of other aspect of programme performance, including timeliness of vaccination. Therefore, it's imperative for countries to not only focus on reaching zero-dose children and improving overall coverage but also to prioritise the measurement of vaccination timeliness, along with assessing the burden, spatial pattern, and determinants associated with it. Doing so will ensure that all children receive the full benefits of vaccines and protect the gains made towards achieving the IA2030 goals.

References

1. World Health Assembly. WHO expanded programme on immunization. 1974. https://iris.who.int/handle/10665/92778.
2. Chan M. The contribution of immunization: saving millions of lives, and more. *Public Health Reports* 2014; **129**: 7-8.
3. Shattock AJ, Johnson HC, Sim SY, et al. Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. *The Lancet* 2024; **403**(10441): 2307-16.
4. Henderson DA. The eradication of smallpox – An overview of the past, present, and future. *Vaccine* 2011; **29**: D7-D9.
5. Lee SE, Greene SA, Burns CC, Tallis G, Wassilak SG, Bolu O. Progress Toward Poliomyelitis Eradication—Worldwide, January 2021–March 2023. *Morbidity and Mortality Weekly Report* 2023; **72**(19): 517.
6. Li X, Mukandavire C, Cucunubá ZM, et al. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. *Lancet* 2021; **397**(10272): 398-408.
7. Ozawa S, Clark S, Portnoy A, Grewal S, Brenzel L, Walker DG. Return on investment from childhood immunization in low-and middle-income countries, 2011–20. *Health Affairs* 2016; **35**(2): 199-207.
8. Keja K, Chan C, Hayden G, Henderson RH. Expanded programme on immunization. *World Health Stat Q* 1988; **41**(2): 59-63.
9. World Health Organization. Immunization Agenda 2030: a global strategy to leave no one behind. Geneva: World Health Organization,; 2021.
10. World Health Organization. 2022 WHO/UNICEF Estimates of National Immunization Coverage. Geneva, Switzerland: WHO and UNICEF, 2023.
11. World Health Organization. More than 140,000 die from measles as cases surge worldwide. 2019. https://www.unicef.org/press-releases/more-140000-die-measles-cases-surge-worldwide (accessed 09 February 2024).
12. Patel MK, Goodson JL, Alexander Jr JP, et al. Progress toward regional measles elimination—worldwide, 2000–2019. *Morbidity and mortality weekly report* 2020; **69**(45): 1700.
13. Thornton J. Measles cases in Europe tripled from 2017 to 2018. *BMJ* 2019; **364**: l634.
14. World Health Organization. Global Vaccine Action Plan 2011-2020. Geneva, Switzerland: World Health Organization,, 2013.
15. Galles NC, Liu PY, Updike RL, et al. Measuring routine childhood vaccination coverage in 204 countries and territories, 1980–2019: a systematic analysis for the Global Burden of Disease Study 2020, Release 1. *The Lancet* 2021; **398**(10299): 503-21.
16. World Health Organization. Regional Office for the Western P. Routine immunization services during the COVID-19 pandemic. CC BY-NC-SA 3.0 IGO: Manila : WHO Regional Office for the Western Pacific, 2020.
17. World Health Organization. Immunization coverage: Fact sheet, No. 378. 2021. https://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage (accessed November 17 2021).
18. Causey K, Fullman N, Sorensen RJD, et al. Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study. *Lancet* 2021; **398**(10299): 522-34.

19. Gavi The Vaccine Alliance. COVID-19 Situation Report #13. . 2020. https://www.gavi.org/news-resources/document-library/covid-19-situation-reports (accessed 09 February 2024).
20. Organization WH. Third round of the global pulse survey on continuity of essential health services during the COVID-19 pandemic: November–December 2021: interim report, 7 February 2022: World Health Organization, 2022.
21. Masresha BG, Luce R, Jr., Shibeshi ME, et al. The performance of routine immunization in selected African countries during the first six months of the COVID-19 pandemic. *Pan Afr Med J* 2020; **37**(Suppl 1): 12.
22. Brolin Ribacke KJ, Saulnier DD, Eriksson A, von Schreeb J. Effects of the West Africa Ebola Virus Disease on Health-Care Utilization - A Systematic Review. *Front Public Health* 2016; **4**: 222.
23. Masresha BG, Luce Jr R, Weldegebriel G, Katsande R, Gasasira A, Mihigo R. The impact of a prolonged ebola outbreak on measles elimination activities in Guinea, Liberia and Sierra Leone, 2014-2015. *The Pan African Medical Journal* 2020; **35**(Suppl 1).
24. World Health Organization. Training for mid-level managers (MLM) module 5: monitoring the immunization system. Geneva, 2008.
25. MacDonald SE, Russell ML, Liu XC, et al. Are we speaking the same language? an argument for the consistent use of terminology and definitions for childhood vaccination indicators. *Hum Vaccin Immunother* 2019; **15**(3): 740-7.
26. World Health Organization. Harmonizing vaccination coverage measures in household surveys: A primer. Geneva, Switzerland: WHO, 2019.
27. Organization WH. Microplanning for immunization service delivery using the Reaching Every District (RED) strategy: World Health Organization, 2009.
28. World Health Organization. Measles and Rubella Strategic Framework 2021–2030. Geneva, Switzerland: World Health Organization,, 2021.
29. Gavi The Vaccine Alliance. Reaching Zero-dose Children. 2024. https://www.gavi.org/our-alliance/strategy/phase-5-2021-2025/equity-goal/zero-dose-children-missed-communities (accessed 12 February 2024).
30. Gavi The Vaccine Alliance. Gavi phase 5 strategy (2021–2025). 2021. https://www.gavi.org/our-alliance/strategy/phase-5-2021-2025 (accessed 30 August 2022).
31. Arsenault C, Harper S, Nandi A, Rodríguez JMM, Hansen PM, Johri M. An equity dashboard to monitor vaccination coverage. *Bulletin of the World Health Organization* 2017; **95**(2): 128.
32. Mosser JF, Gagne-Maynard W, Rao PC, et al. Mapping diphtheria-pertussis-tetanus vaccine coverage in Africa, 2000-2016: a spatial and temporal modelling study. *Lancet* 2019; **393**(10183): 1843-55.
33. Local Burden of Disease Vaccine Coverage Collaborators. Mapping routine measles vaccination in low- and middle-income countries. *Nature* 2021; **589**(7842): 415-9.
34. Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS medicine* 2013; **10**(5): e1001404.
35. Walton S, Cortina-Borja M, Dezateux C, et al. Measuring the timeliness of childhood vaccinations: Using cohort data and routine health records to evaluate quality of immunisation services. *Vaccine* 2017; **35**(51): 7166-73.
36. Jahn A, Floyd S, Mwinuka V, et al. Ascertainment of childhood vaccination histories in northern Malawi. *Tropical medicine & international health* 2008; **13**(1): 129-38.

37. Luman ET, Barker LE, Shaw KM, McCauley MM, Buehler JW, Pickering LK. Timeliness of childhood vaccinations in the United States: days undervaccinated and number of vaccines delayed. *Jama* 2005; **293**(10): 1204-11.

38. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet (London, England)* 2009; **373**(9674): 1543-9.

39. Buttery JP, Graham SM. Immunisation timing: the protective layer in vaccine coverage. *Lancet (London, England)* 2009; **373**(9674): 1499-500.

40. Hardt K, Bonanni P, King S, et al. Vaccine strategies: Optimising outcomes. *Vaccine* 2016; **34**(52): 6691-9.

41. Plotkin SA. Vaccines: Past, present and future. *Nature Medicine* 2005; **11**(4S): S5-S.

42. Nic Lochlainn LM, de Gier B, van der Maas N, et al. Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2019; **19**(11): 1246-54.

43. Henderson DA, Dunston FJ, Fedson DS, et al. The Measles Epidemic: The Problems, Barriers, and Recommendations. *JAMA* 1991; **266**(11): 1547-52.

44. Katfy K, Diawara I, Maaloum F, et al. Pertussis in infants, in their mothers and other contacts in Casablanca, Morocco. *BMC Infectious Diseases* 2020; **20**(1): 43.

45. Wendelboe AM, Njamkepo E, Bourillon A, et al. Transmission of Bordetella pertussis to young infants. *Pediatr Infect Dis J* 2007; **26**(4): 293-9.

46. Borràs E, Urbiztondo L, Costa J, et al. Measles antibodies and response to vaccination in children aged less than 14 months: implications for age of vaccination. *Epidemiol Infect* 2012; **140**(9): 1599-606.

47. Garly ML, Balé C, Martins CL, et al. Measles antibody responses after early two dose trials in Guinea-Bissau with Edmonston-Zagreb and Schwarz standard-titre measles vaccine: better antibody increase from booster dose of the Edmonston-Zagreb vaccine. *Vaccine* 2001; **19**(15-16): 1951-9.

48. Whittle H, Hanlon P, O'Neill K, et al. Trial of high-dose Edmonston-Zagreb measles vaccine in the Gambia: antibody response and side-effects. *Lancet* 1988; **2**(8615): 811-4.

49. Guerra FA. Delays in immunization have potentially serious health consequences. Paediatr Drugs; 2007. p. 143-8.

50. Minetti A, Kagoli M, Katsulukuta A, et al. Lessons and challenges for measles control from unexpected large outbreak, Malawi. *Emerging infectious diseases* 2013; **19**(2): 202-9.

51. Kiely M, Boulianne N, Talbot D, et al. Impact of vaccine delays at the 2, 4, 6 and 12 month visits on incomplete vaccination status by 24 months of age in Quebec, Canada. *BMC Public Health* 2018; **18**(1): 1364.

52. Truelove SA, Graham M, Moss WJ, Metcalf CJE, Ferrari MJ, Lessler J. Characterizing the impact of spatial clustering of susceptibility for measles elimination. *Vaccine* 2019; **37**(5): 732-41.

53. Sanyaolu A, Okorie C, Marinkovic A, et al. Measles Outbreak in Unvaccinated and Partially Vaccinated Children and Adults in the United States and Canada (2018-2019): A Narrative Review of Cases. *Inquiry* 2019; **56**: 46958019894098.

54. Zucker JR, Rosen JB, Iwamoto M, et al. Consequences of Undervaccination — Measles Outbreak, New York City, 2018–2019. *New England Journal of Medicine* 2020; **382**(11): 1009-17.

55. Masters NB, Eisenberg MC, Delamater PL, Kay M, Boulton ML, Zelner J. Fine-scale spatial clustering of measles nonvaccination that increases outbreak potential is obscured by

aggregated reporting data. *Proceedings of the National Academy of Sciences* 2020; **117**(45): 28506-14.

56. Patel MM, Clark AD, Sanderson CF, Tate J, Parashar UD. Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis. *PLoS Med* 2012; **9**(10): e1001330.
57. Worldometer. The Gambia Population. 2021. https://www.worldometers.info/world-population/gambia-population/ (accessed November 19 2021).
58. UNICEF. Key demographic indicators (The Gambia). 2024. https://data.unicef.org/country/gmb/ (accessed 16 February 2024).
59. World Health Organization. History of the measles vaccine. 2023. https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-measles-vaccination (accessed 22 April 2023).
60. Ministry of Health The Gambia. Draft policy of the expanded programme on immunisation, Republic of The Gambia. Banjul, The Gambia: Ministry of Health The Gambia, 2006.
61. World Health Organization. Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination. Geneva, Switzerland: World Health Organization, 2015.
62. Gavi The Vaccine Alliance. Program impact: The Gambia. 2022. https://www.gavi.org/programmes-impact/country-hub/africa/gambia (accessed 27 January 2023).
63. World Health Organization. Gambia: WHO and UNICEF estimates of immunization coverage: 2022 revision. Geneva, Switzerland: World Health Organization, 2023.
64. Wariri O, Nkereuwem E, Erondu NA, et al. A scorecard of progress towards measles elimination in 15 west African countries, 2001–19: a retrospective, multicountry analysis of national immunisation coverage and surveillance data. *The Lancet Global Health* 2021; **9**(3): e280-e90.
65. Wariri O, Edem B, Nkereuwem E, et al. Tracking coverage, dropout and multidimensional equity gaps in immunisation systems in West Africa, 2000-2017. *BMJ Global Health* 2019; **4**(5): e001713-e.
66. Touray E, Barrow A, Kinteh B, et al. Childhood vaccination uptake and associated factors among children 12-23 months in rural settings of the Gambia: a community-based cross-sectional study. *BMC Public Health* 2021; **21**(1): 1740.
67. Scott S, Odutola A, Mackenzie G, et al. Coverage and timing of children's vaccination: an evaluation of the expanded programme on immunisation in The Gambia. *PLoS One* 2014; **9**(9): e107280.
68. UNICEF (The Gambia). Immunisation. 2021. https://www.unicef.org/gambia/immunization (accessed November 17 2021).
69. Miyahara R, Jasseh M, Gomez P, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. *Vaccine* 2016; **34**(29): 3335-41.
70. Odutola A, Afolabi MO, Ogundare EO, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. *BMC health services research* 2015; **15**: 346.
71. World Health Organization. Surveillance for Vaccine Preventable Diseases (VPDs). 2022. https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance/surveillance-for-vpds (accessed 19 July 2022).
72. Sowe A, Njie M, Sowe D, et al. Epidemiology of measles cases, vaccine effectiveness, and performance towards measles elimination in The Gambia. *PLoS One* 2021; **16**(10): e0258961.
73. Joseph NK, Macharia PM, Ouma PO, et al. Spatial access inequities and childhood immunisation uptake in Kenya. *BMC Public Health* 2020; **20**(1): 1407.

74. Okwaraji YB, Mulholland K, Schellenberg JR, Andarge G, Admassu M, Edmond KM. The association between travel time to health facilities and childhood vaccine coverage in rural Ethiopia. A community based cross sectional study. *BMC Public Health* 2012; **12**: 476.

75. GBD 2020 R, Vaccine Coverage Collaborators. Measuring routine childhood vaccination coverage in 204 countries and territories, 1980-2019: a systematic analysis for the Global Burden of Disease Study 2020, Release 1. *Lancet* 2021; **398**(10299): 503-21.

76. World Health Organization Regional Office for Africa. Measles elimination by 2020: a strategy for the African region report of the secretariat. Congo (Brazzaville): World Health Organization, 2011.

77. Masters NB, Wagner AL, Boulton ML. Vaccination timeliness and delay in low- and middle-income countries: a systematic review of the literature, 2007-2017. *Human Vaccines and Immunotherapeutics* 2019; **15**(12): 2790-805.

78. Wariri O, Okomo U, Kwarshak YK, et al. Timeliness of routine childhood vaccination in 103 low-and middle-income countries, 1978–2021: A scoping review to map measurement and methodological gaps. *PLOS Global Public Health* 2022; **2**(7): e0000325.

79. Wariri O, Utazi CE, Okomo U, et al. Timeliness of routine childhood vaccination among 12-35 months old children in The Gambia: Analysis of national immunisation survey data, 2019-2020. *PLoS One* 2023; **18**(7): e0288741.

80. Wariri O, Utazi CE, Okomo U, et al. Mapping the timeliness of routine childhood vaccination in The Gambia: A spatial modelling study. *Vaccine* 2023.

81. Kuylen E, Willem L, Broeckhove J, Beutels P, Hens N. Clustering of susceptible individuals within households can drive measles outbreaks: an individual-based model exploration. *Scientific Reports* 2020; **10**(1): 19645.

82. Wariri O, Utazi CE, Okomo U, et al. Impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in the Gambia, 2015–2021. *BMJ Global Health* 2023; **8**(12): e014225.

83. Ouma PO, Malla L, Wachira BW, et al. Geospatial mapping of timely access to inpatient neonatal care and its relationship to neonatal mortality in Kenya. *PLOS Global Public Health* 2022; **2**(6): e0000216.

84. Skiles MP, Burgert CR, Curtis SL, Spencer J. Geographically linking population and facility surveys: methodological considerations. *Population Health Metrics* 2013; **11**(1): 14.

85. Yoo E-h, Palermo T, Maluka S. Geostatistical linkage of national demographic and health survey data: a case study of Tanzania. *Population Health Metrics* 2021; **19**(1): 42.

86. IHME. Institute for Health Metrics and Evaluation. 2024. https://www.healthdata.org/ (accessed 08 March 2024 2024).

87. Tatem AJ. WorldPop, open data for spatial demography. *Scientific Data* 2017; **4**(1): 170004.

88. Utazi CE, Aheto JMK, Wigley A, et al. Mapping the distribution of zero-dose children to assess the performance of vaccine delivery strategies and their relationships with measles incidence in Nigeria. *Vaccine* 2023; **41**(1): 170-81.

89. Utazi CE, Thorley J, Alegana VA, et al. Mapping vaccination coverage to explore the effects of delivery mechanisms and inform vaccination strategies. *Nat Commun* 2019; **10**(1): 1633.

90. Utazi CE, Thorley J, Alegana VA, et al. High resolution age-structured mapping of childhood vaccination coverage in low and middle income countries. *Vaccine* 2018; **36**(12): 1583-91.

91. Gavi; UNICEF; HealthEnabled. Leveraging geospatial technologies and data to strengthen immunisation programmes: rapid guidance for investment planning, 2021.

92. Thaddeus S, Maine D. Too far to walk: Maternal mortality in context. *Social Science and Medicine* 1994; **38**(8): 1091-110.

93. Phillips DE, Dieleman JL, Lim SS, Shearer J. Determinants of effective vaccine coverage in low and middle-income countries: a systematic review and interpretive synthesis. *BMC Health Services Research* 2017; **17**(1): 681.

94. World Health Organization. Development of tools to measure behavioural and social drivers (BeSD) of vaccination: Progress Report. Geneva, Switzerland: World Health Organization, 2020.

95. Wagai JN, Rhoda D, Prier M, et al. Implementing WHO guidance on conducting and analysing vaccination coverage cluster surveys: Two examples from Nigeria. *PLoS One* 2021; **16**(2): e0247415.

96. Spencer N, Raman S, O'Hare B, Tamburlini G. Addressing inequities in child health and development: towards social justice. *BMJ Paediatr Open* 2019; **3**(1): e000503.

97. Health CoSDo. Closing the gap in a generation: health equity through action on the social determinants of health: final report of the commission on social determinants of health: World Health Organization; 2008.

98. Cassell J, Leach M, Fairhead J, Small M, Mercer C. The social shaping of childhood vaccination practice in rural and urban Gambia. *Health policy and planning* 2006; **21**(5): 373-91.

99. Kirk GD, Lesi OA, Mendy M, et al. The Gambia Liver Cancer Study: Infection with hepatitis B and C and the risk of hepatocellular carcinoma in West Africa. *Hepatology* 2004; **39**(1): 211-9.

100. Payne S, Townend J, Jasseh M, Lowe Jallow Y, Kampmann B. Achieving comprehensive childhood immunization: an analysis of obstacles and opportunities in The Gambia. *Health Policy Plan* 2014; **29**(2): 193-203.

101. Metcalf CJ, Farrar J, Cutts FT, et al. Use of serological surveys to generate key insights into the changing global landscape of infectious disease. *Lancet* 2016; **388**(10045): 728-30.

102. WHO Regional Office for Europe. Guidance on conducting serosurveys in support of measles and rubella elimination in the WHO European Region. Copenhagen Denmark: WHO Regional Office for Europe, 2013.

103. Prada JM, Metcalf CJE, Ferrari MJ. Improving measles incidence inference using age-structured serological data. *Epidemiol Infect* 2018; **146**(13): 1699-706.

104. Cutts FT, Hanson M. Seroepidemiology: an underused tool for designing and monitoring vaccination programmes in low- and middle-income countries. *Trop Med Int Health* 2016; **21**(9): 1086-98.

105. Winter AK, Martinez ME, Cutts FT, et al. Benefits and Challenges in Using Seroprevalence Data to Inform Models for Measles and Rubella Elimination. *The Journal of Infectious Diseases* 2018; **218**(3): 355-64.

106. London School of Hygiene and Tropical Medicine. Dr Oghenebrume Wariri Awarded NIH Emerging Global Leader Award. 2023. https://www.lshtm.ac.uk/research/units/mrc-gambia/news/383581/dr-oghenebrume-wariri-awarded-nih-emerging-global-leader-award (accessed 06 March 2024).

107. Li Y, Vinzamuri B, Reddy CK. Regularized weighted linear regression for high-dimensional censored data. Proceedings of the 2016 SIAM International Conference on Data Mining; 2016: SIAM; 2016. p. 45-53.

108. Oyo-Ita A, Oduwole O, Arikpo D, et al. Interventions for improving coverage of childhood immunisation in low- and middle-income countries. *Cochrane Database of Systematic Reviews* 2023; (12).

109. Abatan B, Agboghoroma O, Akemoke F, et al. Intense and mild first epidemic wave of coronavirus disease, the Gambia. *Emerging infectious diseases* 2021; **27**(8): 2064.

110. Labrique AB, Wadhwani C, Williams KA, et al. Best practices in scaling digital health in low and middle income countries. *Globalization and Health* 2018; **14**(1): 103.

111. Markhof Y, Wollburg P, Zezza A. Are vaccination campaigns misinformed? Experimental evidence from COVID-19 in low-and middle-income countries. The World Bank; 2023.

112. MEASURE Evaluation. Barriers to use of health data in low-and middleincome countries: a review of the literature: MEASURE Evaluation, 2018.

113. de Villiers MJ, Nayagam S, Hallett TB. The impact of the timely birth dose vaccine on the global elimination of hepatitis B. *Nat Commun* 2021; **12**(1): 6223.

Appendices

The appendix features the following items:

1. Appendix 1: Chapter 3 (Published Protocol Paper)
2. Appendix 2: Chapter 3 (research paper S1 Table)
3. Appendix 3: Chapter 3 (research paper S2 Table)
4. Appendix 4: Chapter 3 (research paper PRISMA-ScR Checklist)
5. Appendix 5: Chapter 4 (research paper 1 S1 Figure)
6. Appendix 6: Chapter 4 (research paper 1 S1 Table)
7. Appendix 7: Chapter 4 (research paper 1 S2 Table)
8. Appendix 8: Chapter 4 (Research Paper 2 Supplementary material)
9. Appendix 9: Chapter 5 (Research Paper Supplementary material)
10. Appendix 10: Chapter 6 (Research Paper Supplementary material)
11. Appendix 11: Ethical approval (LSHTM)
12. Appendix 12: Ethical approval (MRC Unit The Gambia at LSHTM)
13. Appendix 13: Links to R Codes developed for data cleaning, wrangling and analysis

Appendix 1: Chapter 3 (Published Protocol Paper)

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1509291	**Title**	DR
First Name(s)	Oghenebrume		
Surname/Family Name	Wariri		
Thesis Title	Timeliness of routine childhood vaccination in The Gambia: examining the burden, spatial pattern, determinants and the impact of COVID-19 pandemic		
Primary Supervisor	Chris Grundy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLoS ONE		
When was the work published?	June 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?
Please list the paper's authors in the intended authorship order:

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was responsible for the conceptualisation of the work, development of the review protocol, including the review methodology, search strategy, inclusion criteria, exclusion criteria and writing of the manuscript for publication.I handled all the referencing, submission, review and response and re-submission process.

SECTION E

Student Signature	[redacted]
Date	20th February 2024

Supervisor Signature	Chris Grundy
Date	21 Feb 2024

PLOS ONE

STUDY PROTOCOL

Timeliness of routine childhood vaccination in low- and middle-income countries, 1978–2021: Protocol for a scoping review to map methodologic gaps and determinants

Oghenebrume Wariri[1,2]*, **Uduak Okomo**[1], **Yakubu Kevin Kwarshak**[3], **Kris A. Murray**[4,5], **Chris Grundy**[2‡], **Beate Kampmann**[1,6‡]

1 Vaccines and Immunity Theme, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, Fajara, The Gambia, **2** Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom, **3** Department of Surgery, Jos University Teaching Hospital, Jos, Nigeria, **4** MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, Fajara, The Gambia, **5** MRC Centre for Global Infectious Disease Analysis, Imperial College School of Public Health, Imperial College London, London, United Kingdom, **6** The Vaccine Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom

‡ These authors are joint senior authors on this work.
* Oghenebrume.Wariri@lshtm.ac.uk

OPEN ACCESS

Citation: Wariri O, Okomo U, Kwarshak YK, Murray KA, Grundy C, Kampmann B (2021) Timeliness of routine childhood vaccination in low- and middle-income countries, 1978–2021: Protocol for a scoping review to map methodologic gaps and determinants. PLoS ONE 16(6): e0253423. https://doi.org/10.1371/journal.pone.0253423

Editor: Charles Shey Wiysonge, South African Medical Research Council, SOUTH AFRICA

Published: June 17, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0253423

Funding: This project is part of the EDCTP2 programme supported by the European Union (grant number TMA2019CDF-2734 - TIMELY). OW is also supported by an Imperial College London Wellcome Trust Institutional Strategic Support Fund (ISSF) (grant no RSRO_P67869). KM is

Abstract

The literature on the timeliness of childhood vaccination (i.e. vaccination at the earliest appropriate age) in low-and middle-income countries has important measurement and methodological issues that may limit their usefulness and cross comparison. We aim to conduct a comprehensive scoping review to map the existing literature with a key focus on how the literature on vaccination timeliness has evolved, how it has been defined or measured, and what determinants have been explored in the period spanning the last four decades. This scoping review protocol was developed based on the guidance for scoping reviews from the Joanna Briggs Institute. We will include English and French language peer-reviewed publications and grey literature on the timeliness of routine childhood vaccination in low-and middle-income countries published between January 1978 through to 2021. A three-step search strategy that involves an initial search of two databases to refine the keywords, a full search of all included electronic databases, and screening of references of previous studies for relevant articles missing from our full search will be employed. The search will be conducted in five electronic databases: MEDLINE, EMBASE, Global Health, CINAHL and Web of Science. Google search will also be conducted to identify relevant grey literature on vaccination timeliness. All retrieved titles from the search will be imported into Endnote X9.3.3 (Clarivate Analytics) and deduplicated. Two reviewers will screen the titles, abstracts and full texts of publications for eligibility using Rayyan–the web based application for screening articles for systematic reviews. Using a tailored data extraction template, we will extract relevant information from eligible studies. The study team will analyse the extracted data using descriptive statistical methods and thematic analysis. The results will be presented using tables, while charts and maps will be used to aid the visualisation of the key findings and themes. The proposed review will generate evidence on key methodological

supported by joint Centre funding from the UK Medical Research Council and Department for International Development [MR/R0156600/1]. The Vaccines and Immunity Theme (OW, UO, and BK) is jointly funded by the UK MRC and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 Programme supported by the EU (MC UP_A900/1122, MC UP A900/115).

Competing interests: The authors have declared that no competing interests exist.

gaps in the literature on timeliness of childhood vaccination. Such evidence would shape the direction of future research, and assist immunisation programme managers and country-level stakeholders to address the needs of their national immunisation system.

Introduction

Since the World Health Organization (WHO) introduced the Expanded Programme on Immunization (EPI) in 1974 [1], the proportion of children protected against vaccine-preventable diseases (VPDs) continue to increase with more than a billion children vaccinated in the last decade alone [2]. Globally, about 2–3 million deaths from diseases such as diphtheria, tetanus, pertussis and measles are prevented yearly with lifesaving childhood vaccines [2]. In low- and middle-income countries (LMICs), current estimates suggest that between 2000 and 2019, 36 million deaths have been averted among children under 5 by vaccination programmes [3]. Although EPI has drastically reduced the incidence of, and deaths from VPDs, its success across and within countries vary, especially in LMICs.

The usual metric employed for assessing the success of immunisation systems is routine vaccination coverage at specific ages [4]. This metric, however, does not take into consideration whether the vaccines have been received in a timely manner, in accordance with the recommended national vaccination windows. Even in the presence of high overall coverage rates, measurement of crude vaccination coverage can mask substantial delays in vaccinations [5]. Timeliness of vaccination (i.e. vaccination at the earliest appropriate age) matters because vaccinations that are received too early or too closely spaced may result in suboptimal immunological responses [6]. On the other hand, delayed childhood vaccination unnecessarily prolongs exposures to VPDs such as pertussis, measles and *Haemophilus influenzae* type b–diseases for which peaks and severity are worse during infancy [6, 7]. Untimely vaccination, therefore, endangers the health of children and compromises herd immunity, with potential implications for VPDs outbreaks irrespective of coverage rates.

Although there is a growing body of literature on timeliness of childhood vaccinations, many studies have focussed on high-income countries where VPD burden is comparatively low. Furthermore, the literature from LMICs have important measurement and methodological issues which may limit their usefulness and cross comparison. For example, there is a lack of a measurement cut-off or agreed-upon definition for what might be considered timely vaccination [8]. While some authors have studied vaccination timeliness using a continuous measure [9–11], others have used categorical, but with varying cut-offs points [12–14]. Second, the determinants of vaccination timeliness have not been robustly researched in the empirical literature which makes it difficult to more clearly define the priority for future research and policy.

To our knowledge, the systematic review by Masters et. al. (2019) was the first to summarise the literature on vaccination timeliness in LMICs to identify methodological gaps and provided recommendations for future studies [8]. While their review has provided important insights into the lack of a uniform definition of what might constitute timely vaccination, there were several limitations that have necessitated a further review. First, EPI was introduced by WHO in 1974 and by 1977 all LMICs had been mandated to adopt the WHO-recommended schedule [1]. The global COVID pandemic has been shown to negatively affect EPI vaccine delivery and acceptance, especially in LMICs. By limiting their review to studies conducted between 2007 and 2017 therefore, important studies conducted before 2007 and after

2017 would have been omitted. Second, their review was conducted in only three electronic databases and restricted to studies published in English language. To bridge this gap, we therefore aim to conduct a more comprehensive scoping review, and map the existing literature on vaccination timeliness with a key focus on the methodological gaps in its definition, measurement, and determinants.

Methods

This protocol was developed based on the guidance for scoping reviews from the Joanna Briggs Institute (JBI) [15]. The scoping review process will be guided by the methodological framework proposed by Arksey and O'Malley [16]. The reporting of the scoping review output will be conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist [17].

Review questions

This scoping review will answer the following key research questions:

1. How has the literature on childhood vaccination timeliness in LMICs evolved (i.e. studies published per year and the antigens studied over time) in the last four decades?
2. In what LMIC countries have the literature on childhood vaccination timeliness been focused?
3. How has childhood vaccination timeliness been defined or measured in the empiric studies from LMICs in the last four decades?
4. What statistical analytic approaches have been used in the literature to assess childhood vaccination timeliness?
5. What determinants or factors contributing to untimely childhood vaccination have been studied in LMICs?

Information sources

We plan this review to identify peer-reviewed and online grey literature on vaccination timeliness in any low-and middle-income country (LMIC) [18]. The search will be conducted in five electronic databases: MEDLINE, EMBASE, Global Health, CINAHL and Web of Science. Using selected terms from the search strategy, Google search will also be conducted to identify relevant grey literature on vaccination timeliness.

Search strategy

As recommended by the JBI, a three-step search strategy will be utilised to ensure that our search is comprehensive [15]. The search strategy was developed in consultation with, and refined based on input from a librarian. First, a preliminary search of MEDLINE and Web of Science was conducted on March 27, 2021 using the key concepts: *Childhood; Vaccination*; *Timeliness*; and *LMICs*. To further refine the search strategy, the initial search was followed by an analysis of the text words in the title and abstract of the retrieved papers and the index terms used in describing the articles. An example of the search strategy and terms used in MEDLINE is included as S1 Table in this protocol. The second step will be a search conducted across all five included databases using the search strategy which has been refined based on all identified keywords and index terms from the first step. The search strategy will be adapted

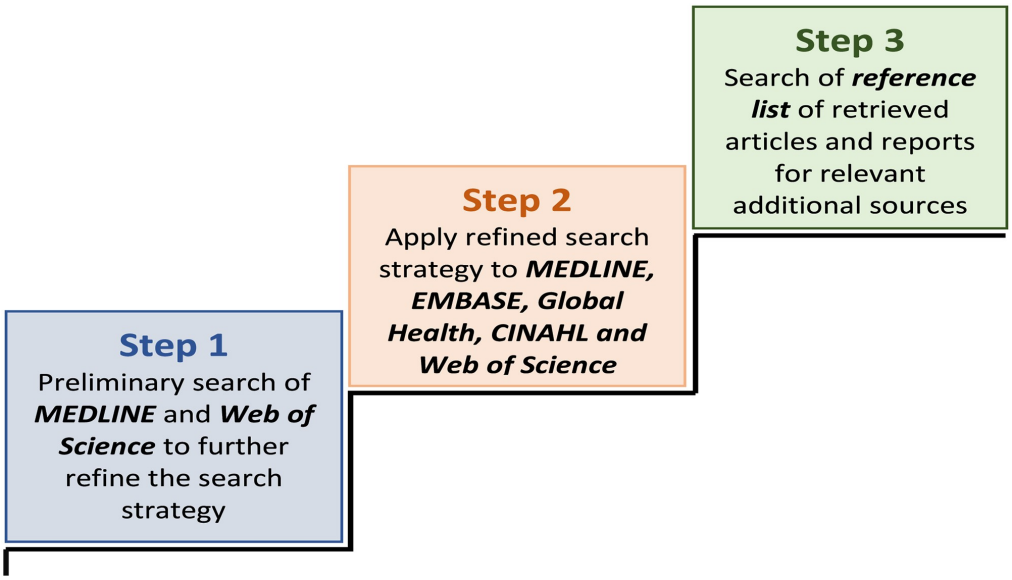


Fig 1. The three-step search strategy that will be utilised to ensure a comprehensive search for the scoping review.

https://doi.org/10.1371/journal.pone.0253423.g001

based on the search terminology for each of the included databases. In the third step, the reference list of all the identified papers and reports will be searched for additional sources. See Fig 1 for illustration of the search strategy.

Inclusion criteria

To ensure comprehensiveness, quantitative or mixed-methods studies or reports will be included if they meet the following criteria: (a) focused on childhood vaccinations that are part of the routine national EPI programme; (b) calculate some measure of timeliness related to vaccine coverage; (c) are conducted on data from countries categorised as LMICs by the World Bank [18]; (d) published in English or French languages; and (e) from January 1978 through to 2021. The decision to restrict this scoping review to studies conducted in LMICs is because of the higher burden of VPDs in these countries and the fact that the national EPI schedule in these countries adopts the WHO-recommended routine childhood immunization schedule, in contrast to many high-income countries. The choice to include studies published from January 1978 is based on the fact that routine childhood immunization against diphtheria, pertussis, tetanus, poliomyelitis, measles and tuberculosis in LMICs commenced in 1977 in many countries [1]. The search will be extended to 2021 to ensure that the latest evidence on vaccination timeliness is included in this review even as the ongoing COVID-19 pandemic has impacted on routine vaccination programmes with potential delayed vaccinations in many LMICs.

Exclusion criteria

Systematic reviews, study protocols, correspondences, journal commentaries, and conference abstracts will be excluded. Additionally, studies which are based on the modelling of vaccination timeliness will also be excluded.

Study selection

All retrieved titles from the search will be imported into Endnote X9.3.3 (Clarivate Analytics) and de-duplication of records will be performed using the Endnote duplicates function. The references will then be exported to Rayyan (a web based application for screening articles for systematic reviews) where two reviewers will screen the titles and abstracts for relevance [19]. In this initial stage, two reviewers will independently screen the titles and abstracts to identify which studies meet eligibility criteria after which the included references will be exported back to Endnote for full-text screening and extraction. In the second stage, one out of the first two reviewers that performed the initial assessment will screen the full-text of the included studies to verify if they will be appropriate for full data extraction while the second reviewer will verify all decisions. During this stage, some articles will be excluded from full data extraction if they do not meet the inclusion/exclusion criteria. The pre-specified inclusion criteria in this protocol will guide article selection for inclusion. All decisions related to article inclusion will be made through consensus by the two reviewers conducting the extraction. However, if the two reviewers fail to reach a consensus, a third member of the review team will be consulted to help resolve the disagreement. The process and outcome of screening, inclusion, and exclusion of articles will be illustrated using the PRISMA flow chart diagram for reporting items for systematic reviews.

Data extraction

A data extraction template has been developed which will be used to record the information of interest from the included articles. This template was adapted from the JBI data extraction tool for scoping reviews [20]. Two members of the review team have piloted and refined the data extraction template on 20 randomly selected articles during the protocol development stage as recommended by Arksey & O'Malley [16] and the JBI [20]. The key information to be extracted is listed in Box 1 below. During the full data extraction process, one reviewer will extract the data while another reviewer will verify the extracted data to ensure the quality of the data. Critical appraisal of the included studies will not be conducted because it is not mandatory for scoping reviews [20].

Box 1. Key information in the data extraction template

1. Author (lead author only and et.al.)
2. Year of study publication
3. Source/country of origin of the study (list all the countries)
4. Study population (i.e. age range of children included)
5. Methodology or study design (e.g. cross sectional, cohort, etc.)
6. Dataset used (e.g. Health survey data, surveillance data, etc.)
7. Routine EPI vaccines/antigens studied (i.e. indicate names of the antigen)
8. How vaccination timeliness was measured (e.g. continuous measures, categorical measures, etc.)

9. Statistical analysis approach employed
10. Determinants or factors contributing to vaccination timeliness that were explored

Presentation and charting of results

The extracted data will be analysed using descriptive statistical methods. The results will be presented using tables, while charts and maps will be used to aid the visualisation of the key findings. The information to be captured with a table include the lead author, study population, study design, the dataset used among other variables. The year of study publication will be summarised using a line graph showing trends since 1978, while the number of studies published per country will be represented using a thematic map. The determinants of vaccination timeliness will be organised according to *a priori* categories that have been developed based on the three-delays conceptual framework by Thaddeus and Maine [21]. All results will be presented using a narrative summary according to the objectives of this scoping review.

Ethics

Ethical approval is not required for scoping review because it involves the synthesis of publicly available publications. Pre-registration in a public registry such as PROSPERO is not mandatory for scoping review protocols.

Discussion

The proposed scoping review is expected to map the existing literature on the timeliness of vaccination in LMICs from 1978 through 2021, with a focus on how the literature has evolved, in what geographic context, its definition, and determinants. Specifically, the review seeks to map how timeliness of childhood vaccination has been conceptualised or measured in the literature. Mapping the evidence on how vaccination timeliness has been measured in LMICs over the past four decades will highlight critical methodological gaps that will aid future research to adopt a more robust measurement of vaccination timeliness.

Mapping the evidence to show which determinants have been previously or more routinely explored in the literature will highlight the potential research gaps related to the determinants of childhood vaccination timeliness. There is emerging evidence that shows that supply-side factors such as geographic accessibility (travel time, distance to facility, etc.) to immunisation service points impacts the likelihood of receiving childhood vaccination. Yet, to the best of our knowledge, the influence of geographic accessibility on the timeliness of childhood vaccination has been less explored in the literature in LMIC [22, 23]. Such a gap limits the availability of critical evidence that could assist immunisation programme managers and country-level stakeholders to address the needs of EPI.

A limitation of this scoping review is that it will not include studies from high-income countries, and studies that are based on vaccinations not given within the remit of the routine EPI schedule such as those given in adolescence, adulthood, and even the recent COVID-19 vaccination. While it is important to study the timeliness of vaccination in these contexts, we will focus on routine childhood vaccination in LMICs for two reasons. First, LMICs have the highest burden of VPDs which makes it imperative for the EPI vaccines to be received within the predetermined vaccination windows. Second, the peak and severity of VPDs is worse

during early childhood or infancy which further highlight the need for receipt of vaccines against VPDs in an age-appropriate manner, before the peak of exposures. Despite the limitations highlighted above, the proposed scoping review, when completed, will provide robust evidence on the methodological gaps in the literature on vaccination timeliness in LMICs spanning more than four decades. The results would aid the design and conduct of future empirical studies into the timeliness of routine childhood vaccinations, thus, ensuring the usefulness and cross comparison of their output.

Supporting information

S1 Table. Example of the full search strategy and terms developed for use in MEDLINE.
(DOCX)

S1 Checklist. PRISMA-ScR fillable checklist.
(DOCX)

Author Contributions

Conceptualization: Oghenebrume Wariri.

Funding acquisition: Oghenebrume Wariri.

Investigation: Oghenebrume Wariri, Uduak Okomo, Yakubu Kevin Kwarshak.

Methodology: Oghenebrume Wariri, Uduak Okomo, Yakubu Kevin Kwarshak, Kris A. Murray, Chris Grundy, Beate Kampmann.

Project administration: Oghenebrume Wariri.

Resources: Oghenebrume Wariri.

Supervision: Uduak Okomo, Kris A. Murray, Chris Grundy, Beate Kampmann.

Validation: Yakubu Kevin Kwarshak.

Writing – original draft: Oghenebrume Wariri.

Writing – review & editing: Oghenebrume Wariri, Uduak Okomo, Yakubu Kevin Kwarshak, Kris A. Murray, Chris Grundy, Beate Kampmann.

References

1. Keja K, Chan C, Hayden G, Henderson RH. Expanded programme on immunization. World Health Stat Q. 1988; 41(2):59–63. PMID: 3176515
2. Word Health Organization. Immunization coverage: Fact sheet, No. 378. [cited 2021 March 25]. https://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage.
3. Li X, Mukandavire C, Cucunubá ZM, Echeverria Londono S, Abbas K, Clapham HE, et al. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Lancet. 2021; 397(10272):398–408.
4. Word Health Organization. Training for mid-level managers (MLM) module 5: Monitoring the immunization system. Geneva: World Health Organization, 2008.
5. Walton S, Cortina-Borja M, Dezateux C, Griffiths LJ, Tingay K, Akbari A, et al. Measuring the timeliness of childhood vaccinations: Using cohort data and routine health records to evaluate quality of immunisation services. Vaccine. 2017; 35(51):7166–73. https://doi.org/10.1016/j.vaccine.2017.10.085 PMID: 29132992
6. Plotkin SA. Vaccines: Past, present and future. Nature Medicine. 2005; 11(4S):S5–S. https://doi.org/10.1038/nm1209 PMID: 15812490
7. Guerra FA. Delays in immunization have potentially serious health consequences. Paediatr Drugs; 2007. p. 143–8. https://doi.org/10.2165/00148581-200709030-00002 PMID: 17523694

8. Masters NB, Wagner AL, Boulton ML. Vaccination timeliness and delay in low- and middle-income countries: a systematic review of the literature, 2007–2017. Human Vaccines & Immunotherapeutics. 2019; 15(12):2790–805. https://doi.org/10.1080/21645515.2019.1616503 PMID: 31070992

9. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. The Lancet. 2009; 373(9674):1543–9. https://doi.org/10.1016/S0140-6736(09)60317-2 PMID: 19303633

10. Fadnes LT, Jackson D, Engebretsen IM, Zembe W, Sanders D, Sommerfelt H, et al. Vaccination coverage and timeliness in three South African areas: a prospective study. BMC Public Health. 2011; 11:404. https://doi.org/10.1186/1471-2458-11-404 PMID: 21619642

11. Babirye JN, Engebretsen IM, Makumbi F, Fadnes LT, Wamani H, Tylleskar T, et al. Timeliness of childhood vaccinations in Kampala Uganda: a community-based cross-sectional study. PLoS ONE 2012; 7(4):e35432. https://doi.org/10.1371/journal.pone.0035432 PMID: 22539972

12. Odutola A, Afolabi MO, Ogundare EO, Lowe-Jallow YN, Worwui A, Okebe J, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. BMC Health Services Research. 2015; 15(1):346-. https://doi.org/10.1186/s12913-015-1015-9 PMID: 26315547

13. Miyahara R, Jasseh M, Gomez P, Shimakawa Y, Greenwood B, Keita K, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. Vaccine. 2016; 34(29):3335–41. https://doi.org/10.1016/j.vaccine.2016.05.017 PMID: 27195759

14. Flannery B, Samad S, de Moraes JC, Tate JE, Danovaro-Holliday MC, de Oliveira LH, et al. Uptake of oral rotavirus vaccine and timeliness of routine immunization in Brazil's National Immunization Program. Vaccine. 2013; 31(11):1523–8. https://doi.org/10.1016/j.vaccine.2013.01.004 PMID: 23313652

15. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. JBI Evidence Implementation. 2015; 13(3). https://doi.org/10.1097/XEB.0000000000000050 PMID: 26134548

16. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology. 2005; 8(1):19–32.

17. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018; 169(7):467–73. https://doi.org/10.7326/M18-0850 PMID: 30178033

18. The World Bank. World Bank Country and Lending Groups 2019 [https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

19. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016; 5(1):210. https://doi.org/10.1186/s13643-016-0384-4 PMID: 27919275

20. Joanna Briggs Institute. Data extraction. JBI's Reviewers Manual for Evidence Synthesis 2019 [cited 2021 March 217]. https://wiki.jbi.global/display/MANUAL/11.2.7+Data+extraction.

21. Thaddeus S, Maine D. Too far to walk: Maternal mortality in context. Social Science and Medicine. 1994; 38(8):1091–110. https://doi.org/10.1016/0277-9536(94)90226-7 PMID: 8042057

22. Joseph NK, Macharia PM, Ouma PO, Mumo J, Jalang'o R, Wagacha PW, et al. Spatial access inequities and childhood immunisation uptake in Kenya. BMC Public Health. 2020; 20(1):1407. https://doi.org/10.1186/s12889-020-09486-8 PMID: 32933501

23. Okwaraji YB, Mulholland K, Schellenberg J, Andarge G, Admassu M, Edmond KM. The association between travel time to health facilities and childhood vaccine coverage in rural Ethiopia. A community based cross sectional study. BMC Public Health. 2012; 12(1):476-.

Appendix 2: Chapter 3 (Research Paper S1 Table)

Full search strategy in MEDLINE (Ovid)

Search conducted on 01 July, 2021.

Search	Query	Records retrieved
#1 (Childhood)	Child, preschool[Mesh] OR exp Infant[Mesh] OR infant*[tw] OR child*[tw] OR babies[tw] OR newborn*[tw]	3,208,329
#2 (Vaccination)	Immunization[Mesh] OR immunization schedule[Mesh] OR vaccination[Mesh] OR mass vaccination[Mesh] OR vaccin*[tw] OR immuni#ation*[tw] OR EPI[tw]	495,076
#3 (Timeliness)	Time Factors[Mesh] OR timeliness[tw] OR timing*[tw] OR delay*[tw] OR age-appropriate[tw] OR “on time”[tw] OR untimely[tw] OR timely[tw]	1,898,402
#4 (LMICs)	Developing Countries/ OR ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies))[tiab] OR ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world))[tiab] OR (low* adj (gdp or gnp or gross domestic or gross national))[tiab] OR (low adj3 middle adj3 countr*)[tiab] OR (lmic or lmics or third world or lami countr*)[tiab] OR transitional countr*[tiab] OR global south[tiab] OR Democratic People's Republic of Korea"/ OR (North Korea or (Democratic People* Republic adj2 Korea))[tiab] OR Cambodia/ OR Cambodia[tiab] OR Indonesia/ OR (Indonesia or Dutch East Indies)[tiab] OR (Kiribati or Gilbert Islands or Phoenix Islands or Line Islands)[tiab] OR Laos/ OR (Laos or (Lao adj1 Democratic Republic))[tiab] OR Micronesia/ OR Micronesia[tiab] OR Mongolia/ OR Mongolia[tiab] OR Myanmar/ OR (Myanmar or Burma)[tiab] OR Papua New Guinea/ OR (Papua New Guinea or German New Guinea or British New Guinea or Territory of Papua)[tiab] OR Philippines/ OR (Philippines or Philippine Islands)[tiab] OR Solomon Islands[tiab] OR Timor-Leste/ OR (Timor-Leste or East Timor or Portuguese Timor)[tiab] OR Vanuatu/ OR (Vanuatu or New Hebrides)[tiab] OR Vietnam/ OR (Viet Nam or Vietnam or French Indochina)[tiab] OR American Samoa/ OR American Samoa[tiab] OR exp China/ OR China[tiab] OR Fiji/ OR Fiji[tiab] OR Malaysia/ OR (Malaysia or Malayan Union or Malaya)[tiab] OR Marshall Islands[tiab] OR Nauru.t[iab] OR "Independent State of Samoa"/ OR ((Samoa not American Samoa) or Western Samoa or Navigator Islands or Samoan Islands)[tiab] OR Thailand/ OR (Thailand or Siam)[tiab] OR Tonga/ OR Tonga[tiab] OR (Tuvalu or Ellice Islands)[tiab] OR Melanesia/ OR Melanesia[tiab] OR Polynesia/ OR Polynesia[tiab] OR Kyrgyzstan/ OR Kyrgyzstan or Kyrgyz Republic or Kirghizia or Kirghiz)[tiab] OR Moldova/ OR Moldova[tiab] OR Ukraine/ OR Ukraine[tiab] OR Uzbekistan/ OR Uzbekistan[tiab] OR Albania/ OR Albania[tiab] OR Armenia/ OR Armenia[tiab] OR Azerbaijan/ OR Azerbaijan[tiab] OR "Republic of Belarus"/ OR (Belarus or	

	Byelarus or Byelorussia or Belorussia)[tiab] OR Bosnia-Herzegovina/ OR (Bosnia or Herzegovina)[tiab] OR Bulgaria/ OR Bulgaria[tiab] OR "Georgia (Republic)"/ OR Georgia[tiab] not Georgia/ OR Kazakhstan/ OR (Kazakhstan or Kazakh)[tiab] OR Kosovo/ OR Kosovo[tiab] OR Montenegro/ OR Montenegro[tiab] OR "Republic of North Macedonia"/ OR North Macedonia[tiab] OR Romania/ OR Romania[tiab] OR exp Russia/ OR "Russia (Pre-1917)"/ OR USSR/ OR (Russia or Russian Federation or USSR or Union of Soviet Socialist Republics or Soviet Union)[tiab] OR Serbia/ OR Serbia[tiab] OR Turkey/ OR (Turkey.[tiab] not animal/) or (Anatolia or Asia Minor)[tiab] OR Turkmenistan/ OR Turkmenistan[tiab] OR Tajikistan/ OR Tajikistan[tiab] OR Asia, Central/ OR Asia, Northern/ OR Central Asia[tiab] OR Haiti/ OR (Haiti or Hayti)[tiab] OR Bolivia/ OR Bolivia[tiab] OR El Salvador/ OR El Salvador[tiab] OR Honduras/ OR Honduras[tiab] OR Nicaragua/ OR Nicaragua[tiab] OR Argentina/ OR (Argentina or Argentine Republic)[tiab] OR Belize/ OR Belize or British Honduras)[tiab] OR Brazil/ OR Brazil[tiab] OR Colombia/ OR Colombia[tiab] OR Costa Rica/ OR Costa Rica[tiab] OR Cuba/ OR Cuba[tiab] OR Dominica/ OR Dominica[tiab] OR Dominica[tiab] OR Dominican Republic/ OR Dominican Republic[tiab] OR Ecuador/ OR Ecuador[tiab] OR Grenada/ OR Grenada[tiab] OR Guatemala/ OR Guatemala[tiab] OR Guyana/ OR (Guyana or British Guiana)[tiab] OR Jamaica/ OR Jamaica[tiab] OR Mexico/ OR (Mexico or United Mexican States)[tiab] OR Paraguay/ OR Paraguay.mp OR Peru/ OR Peru[tiab] OR Saint Lucia/ OR (St Lucia or Saint Lucia or Iyonala or Hewanorra)[tiab] OR "Saint Vincent and the Grenadines"/ OR (Saint Vincent or St Vincent or Grenadines)[tiab] OR Suriname/ OR (Suriname or Dutch Guiana)[tiab] OR Venezuela/ OR Venezuela[tiab] OR Djibouti/ OR (Djibouti or French Somaliland)[tiab] OR Egypt/ OR Egypt[tiab] OR Morocco/ OR Morocco[tiab] OR Tunisia/ OR Tunisia.mp OR (Gaza or West Bank or Palestine)[tiab] OR Algeria/ OR Algeria[tiab] OR Iran/ OR (Iran or Persia)[tiab] OR Iraq/ OR (Iraq or Mesopotamia)[tiab] OR Jordan/ OR Jordan[tiab] OR Lebanon/ OR (Lebanon or Lebanese Republic)[tiab] OR Libya/ OR Libya[tiab] Or Syria/ OR (Syria or Syrian Arab Republic)[tiab] OR Yemen/ OR Yemen[tiab] OR Afghanistan/ OR Afghanistan[tiab] OR Nepal/ OR Nepal[tiab] OR Bangladesh/ OR Bangladesh[tiab] OR Bhutan/ OR Bhutan[tiab] OR exp India/ OR India[tiab] OR Pakistan/ OR Pakistan[tiab] OR Maldives[tiab] OR Sri Lanka/ OR (Sri Lanka or Ceylon)[tiab] OR Angola/ OR Angola[tiab] OR Cameroon/ OR (Cameroon or Kamerun or Cameroun)[tiab] OR Cape Verde/ Or (Cape Verde or Cabo Verde)[tiab] OR Comoros/ OR (Comoros or Glorioso Islands or Mayotte)[tiab] OR Congo/ OR (Congo not ((Democratic Republic adj3 Congo) or congo red or crimean-congo))[tiab] OR Cote d'Ivoire/ OR Cote d'Ivoire or Cote dIvoire or Ivory Coast)[tiab] OR Eswatini/ OR (eSwatini or Swaziland)[tiab] OR Ghana/ OR (Ghana or Gold Coast)[tiab] OR Kenya/ OR (Kenya or East Africa Protectorate)[tiab] OR Lesotho/ OR (Lesotho or Basutoland)[tiab] OR Mauritania/ OR Mauritania[tiab] OR Nigeria/ OR Nigeria[tiab] OR (Sao Tome abj2 Principe)[tiab] OR Senegal/ OR Senegal[tiab] OR Sudan/ OR (Sudan not South Sudan)[tiab] OR Zambia/ OR Zambia or Northern Rhodesia)[ti,ab] OR Zimbabwe/ OR (Zimbabwe or Southern Rhodesia)[tiab] OR Botswana/ OR (Botswana or Bechuanaland or Kalahari)[tiab] OR Equitorial Guinea/ OR (Equatorial Guinea or Spanish Guinea)[tiab] OR Gabon/ OR (Gabon or Gabonese Republic)[tiab] OR Mauritius/ OR (Mauritius or Agalega	

	Islands)[tiab] OR Namibia/ OR (Namibia or German South West Africa)[tiab] OR South Africa/ OR (South Africa or Cape Colony or British Bechuanaland or Boer Republics or Zululand or Transvaal or Natalia Republic or Orange Free State)[tiab] OR Benin/ OR (Benin or Dahomey)[tiab] OR Burkna Faso/ OR (Burkina Faso or Burkina Fasso or Upper Volta)[tiab] OR Burundi/ OR (Burundi or Ruanda-Urundi)[tiab] OR Central African Republic/ OR (Central African Republic or Ubangi-Shari)[tiab] OR Chad/ OR Chad[tiab] OR "Democratic Republic of the Congo"/ OR (((Democratic Republic or DR) adj2 Congo) or Congo-Kinshasa or Belgian Congo or Zaire or Congo Free State)[tiab] OR Eritrea/ OR Eritrea[tiab] OR Ethiopia/ OR (Ethiopia or Abyssinia)[tiab] OR Gambia/ OR Gambia[tiab] OR Guinea/ OR (Guinea not (New Guinea or Guinea Pig* or Guinea Fowl or Guinea-Bissau or Portuguese Guinea or Equatorial Guinea))[tiab] OR Guinea-Bissau/ OR (Guinea-Bissau or Portuguese Guinea)[tiab] OR Liberia/ OR Liberia[tiab] OR Madagascar/ OR (Madagascar or Malagasy Republic)[tiab] OR Malawi/ OR (Malawi or Nyasaland)[tiab] OR Mali/ OR Mali[tiab] OR Mozambique/ OR (Mozambique or Mocambique or Portuguese East Africa)[tiab] OR Niger/ OR (Niger not (Aspergillus or Peptococcus or Schizothorax or Cruciferae or Gobius or Lasius or Agelastes or Melanosuchus or radish or Parastromateus or Orius or Apergillus or Parastromateus or Stomoxys))[tiab] OR Rwanda/ OR (Rwanda or Ruanda)[tiab] OR Sierra Leone/ OR (Sierra Leone or Salone)[tiab] OR Somalia/ OR (Somalia or Somaliland)[tiab] OR South Sudan/ OR South Sudan[tiab] OR Tanzania/ OR (Tanzania or Tanganyika or Zanzibar)[tiab] OR Togo/ OR (Togo or Togolese Republic or Togoland)[tiab] OR Uganda/ OR Uganda[tiab] OR "africa south of the sahara"/ OR africa, central/ OR africa, eastern/ OR africa, southern/ OR africa, western/ OR ("Africa South of the Sahara" or sub-Saharan Africa or subSaharan Africa)[tiab] OR Central Africa[tiab] OR Eastern Africa[tiab] OR Southern Africa[tiab] OR Western Africa[tiab]	1,575,940
	#1 AND #2 AND #3 AND #4	2,463
Limited to: 1978 – 2021, English and French language.		**2,153**

Appendix 3: Chapter 3 (Research Paper S2 Table)

Summary characteristics of included studies

Author (s)	Year published	Low-and middle-income country studied	Age group studied	Study methodology	Dataset used for the analysis
Abidin et al	2017	Malaysia	0-5 years	cross sectional	facility-based
Adetifa et al	2018	Kenya	12-23 months	cross sectional	community-based
Agopian et al	2020	Armenia	0-35months	cross sectional	community-based
Akmatov et al	2015	Burkina Faso, Tanzania Benin, Burundi, Cameroon, Chad, Congo Democratic Republic, Côte d'Ivoire, Ethiopia, Gabon, Ghana, Guinea, Kenya, Lesotho, Liberia, Malawi, Mali, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Swaziland, Uganda, Zambia Congo Zimbabwe	0-5 years	cross sectional	community-based
Akmatov et al	2012	Albania, Bangladesh, Belarus, Belize, Bosnia and Herzegovina, Burkina Faso, Burundi, Cameroon, Cote d'Ivoire, Djibouti, Gambia, Ghana, Guinea-Bissau, Guy ana, Iraq, Jamaica, Kazakhstan, Laos, Macedonia, Malawi, Mauritania, Mongolia, Montenegro, Serbia, Sierra Leone, Syria, Thailand, Togo, Trinidad and Tobago, Vietnam, Yemen	0-59 months	cross sectional	community-based
Alam et al	2021	Bangladesh	unclear	cross sectional	facility-based
Ali et al	2019	Iraq	1-2 years	cross sectional	facility-based
Alkoshi et al	2020	Libya	0-18 months	cross sectional	facility-based
Alrowali et al	2019	Saudi Arabia	0-23 months	cross sectional	facility-based
Al-shemari et al	2006	Iraq	0-48 months	cross sectional	facility-based
Alsuhaibani	2020	Saudi Arabia	0-24months	cross sectional	community-based
An et al	2016	Vietnam	0-5 years	cross sectional	community-based
Anbesu et al	2021	Ethiopia	0-11 months	cross sectional	community-based
Ateudjieu et al	2020	Cameroon	0-59 months	cross sectional	facility-based
Awafeso et al	2013	India	12-23 months	cross sectional	community-based

Babirye et al	2012	Uganda	10-23 months	cross sectional	community-based
Bangure et al	2015	Zimbabwe	unclear	RCT	facility-based
Banjari et al	2018	Saudi Arabia	0-35 months	cross sectional	facility-based
Banwat et al	2014	Nigeria	0-12 months	RCT	community-based
Barman et al	2015	India	12-36 months	cross sectional	community-based
Belmar-george	2018	Saint Lucia	9-14 years	cross sectional	community-based
Bicaba et al	2009	Burkina Faso	0-23 months	cross sectional	community-based
Bondo et al	2018	Malawi	2 - 16 months	cross sectional	facility-based
Borus et al	2004	Kenya	0-2 years	cross sectional	facility-based
Boulton et al	2019	Ethiopia	1-5 years	cross sectional	community-based
Calhoum et al	2014	Kenya	12-23 months	cross sectional	community-based
Chen et al	2019	Uganda	0-71 months	cross sectional	facility-based
Chiabi et al	2017	Cameroon	0-11 months	cross sectional	facility-based
Choudhary et al	2018	India	6-11 months	case-control	community-based
Choudhary et al	2019	India	10 -23 months	cross sectional	community-based
Chung et al	2016	China	> 12 months	cross sectional	community-based
Clark et al	2009	Bangladesh, Benin, Bolivia, Brazil, Burkina Faso, Cambodia, Cameroon, Chad, Colombia, Comoros, Congo, Côte d'Ivoire, Dominican Republic, Egypt, Eritrea, Gabon, Ghana, Guatemala, Guinea, Haiti, Honduras, India, Kenya, Kyrgyz Republic, Lesotho, Madagascar, Malawi, Mali, Mauritania, Morocco, Mozambique, Namibia, Nicaragua, Niger, Nigeria, Peru, Rwanda, Senegal, Tanzania, Togo, Turkey, Uganda, Uzbekistan, Yemen, Zambia	0-5 years	cross sectional	community-based
Corsi et al	2009	India	0-5 years	cross sectional	community-based
Cui et al	2010	China	unclear	cross sectional	community-based
Cui et al	2007	China	12-23 months	cross sectional	community-based
Cutts et al	1991	Guinea, Mozambique	12-23 months	cross sectional	community-based
Danjuma et al	2020	Nigeria	newborns	cross sectional	facility-based
D'ardenne et al	2016	Guatemala, Peru	0-5 years	cross sectional	community-based

Datar et al	2005	India	2-35 months	cross sectional	community-based
Dayan et al	2006	Argentina	13-59 months	cross sectional	community-based
Delrieu et al	2015	Burkina Faso, Ghana, Kenya, Senegal, Tanzania	0-5 years	cross sectional	community-based
Dionne-odom et al	2018	Cameroon	12-60 months	cross sectional	community-based
Domek et al	2019	Guatemala	2 - 6 months	RCT	facility-based
Edstam et al	2002	Mongolia	2 years	cross sectional	facility-based
Ettarh et al	2012	Kenya	9-59 months	cross sectional	community-based
Fadnes et al	2011	South Africa	0-2 years	RCT	community-based
Fadnes et al	2011	Uganda	0-2 years	RCT	community-based
Fisker et al	2014	Guinea-Bissau	12-47 months	cohort	community-based
Flannery et al	2013	Brazil	19-36 months	cross sectional	community-based
Gentile et al	2015	Argentina	6-24 months	cross sectional	facility-based
Gibson et al	2017	Kenya	0-12 months	RCT	facility-based
Gibson et al	2015	Kenya	12-23 months	cross sectional	community-based
Gil et al	2015	India	0-12 months	cross sectional	community-based
Giao et al	2019	Vietnam	12-24 months	cross sectional	facility-based
Gram et al	2014	Ghana	0-11 months	cross sectional	community-based
Gunning et al	2020	Zambia	0-12months	cohort	facility-based
Hafele et al	2020	Laos	8-28months	cross sectional	facility-based
Han et al	2014	China	12-59 months	cross sectional	community-based
Hasanain et al	2002	Saudi Arabia	2-52 months	cross sectional	facility-based
He et al	2021	China	1-6 years	cohort	facility-based
Hoest et al	2017	Bangladesh, Brazil, India, Nepal, Peru, Pakistan, South Africa, Tanzania	0-24 months	cross sectional	community-based
Holambe et al	2013	India	infants	cross sectional	facility-based
Hu et al	2017	China	6 months - 3 years	cross sectional	HIMS data
Hu et al	2013	China	18-48 months	cross sectional	community-based
Hu et al	2017	China	24-35 months	cross sectional	community-based
Hu et al	2015	China	> 12 months	cross sectional	community-based
Hu et al	2018	China	24-35 months	cross sectional	community-based

Hu et al	2020	China	12-23 months	cross sectional	community-based
Hu et al	2018	China	0-26 months	cross sectional	HIMS data
Hu et al	2018	China	24-35 months	cross sectional	community-based
Hu et al	2014	China	> 12 months	cross sectional	community-based
Huges et al	2016	Nepal	0-6 months	cohort	community-based
Hutin et al	2013	China	unclear	cross sectional	community-based
Hyunh	2021	Vietnam	12-24 months	cross sectional	facility-based
Ibraheem et al	2019	Nigeria	0-12months	cross sectional	facility-based
Igarashi et al	2010	Zambia	unclear	cross sectional	community-based
Jadidi et al	2015	Iran	24-47 months	cohort	community-based
Jahn et al	2008	Malawi	0-5 years	cross sectional	community-based
Jain et al	2021	India	0-12 months	cross sectional	community-based
Janusz et al	2021	Angola, Burkina Faso, Benin, Burundi, Congo Democratic Republic, Congo, Cote D'Ivoire, Cameroon, Ethiopia, Gabon, Ghana, Gambia, Guinea, Kenya, Comoros, Liberia, Lesotho, Mali, Malawi, Mozambique, Nigeria, Niger, Namibia, Rwanda, Sierra Leone, Senegal, Chad, Togo, Tanzania, Uganda, South Africa, Zambia, Zimbabwe	12-35 months	cross sectional	community-based
Jones et al	2021	Madagascar	0-23 months	cross sectional	facility-based
Kagucia et al	2021	Kenya	0-6 months	RCT	facility-based
Kahn et al	1995	Central African Republic	12-23 months	cross sectional	community-based
Kaji et al	2016	Thailand	migrant children	cohort	school-based
Kang et al	2014	China	7-10 months	cross sectional	community-based
Kidanne et al	2019	Ethiopia	12-23 months	cross sectional	community-based
Kumar et al	2017	India	12-23 months	cross sectional	community-based
Kuruvilla et al	2009	India	12-24 months	cross sectional	community-based
Kyuregyan et al	2021	Russia	0-12 months	cross sectional	mixed
Laryea et al	2014	Ghana	2-28 months	cross sectional	facility-based
Laus`evie et al	2009	Montenegro	22-34 months	cross sectional	facility-based
Levine et al	2021	Ghana	0-12 months	RCT	community-based

Li et al	2020	Kenya	0-23months	cross sectional	community-based
Li et al	2021	China	0-6 years	cross sectional	facility-based
Li et al	2014	China	1-7 years	cross sectional	HIMS data
Li et al	2017	China	infants	cross sectional	facility-based
Li et al	2020	China	8-24months	cross sectional	facility-based
Lin et al	2014	China	9 months - 2 years	case-control	HIMS data
Lindqvist et al	2019	Sri Lanka	0-5years	cross sectional	facility-based
Liu et al	2018	China	0-35 months	cross sectional	community-based
Lopez et al	2018	Philippines	5-6 years	cross sectional	community-based
Loy et al	2020	Singapore	0-24months	cohort	HIMS data
Lugollo et al	2008	Brazil	unclear	case-control	community-based
Luz et al	2016	Colombia	6 months -8 years	cross sectional	community-based
Mansour et al	2018	Lebanon	12-59 months	cross sectional	community-based
Marban-castro et al	2018	Mozambique	0-3years	cross sectional	community-based
Marefiaw et al	2019	Ethiopia	12-23 months	cross sectional	community-based
Master et al	2018	Ethiopia	3-12 months	cross sectional	community-based
Masters et al	2018	Kenya	1-4 years	cross sectional	community-based
Mbengue et al	2017	Senegal	12-23 months	cross sectional	community-based
Mekonnen et al	2020	Ethiopia	12-23 months	cross sectional	community-based
Mekonnen et al	2021	Ethiopia	unclear	RCT	facility-based
Mensah et al	2019	Madagascar	unclear	cross sectional	community-based
Miyahara et al	2016	Gambia	unclear	cross sectional	community-based
Mohammedbeigi et al	2015	Iran	24-47 months	cohort	community-based
Mohhtari et al	2015	Iran	24-47 months	cohort	community-based
Moisi et al	2010	Kenya	unclear	cross sectional	community-based
Monrgomery et al	2015	China	> 8 months	cross sectional	community-based
Moturi et al	2018	Botswana, Gambia, Namibia, Nigeria, Sao Tome and Principi	newborns	cross sectional	facility-based
Mthiyane et al	2019	South Africa	12-59months	cross sectional	community-based
Musa et al	2021	Bosnia and Herzegovina	12-35 months	cross sectional	facility-based

Mutua et al	2015	Kenya	unclear	cohort	community-based
Mutua et al	2021	Angola, Benin, Burkina Faso, Burundi, Central African Republic, Cameroon, Chad, Comoros, Congo, Congo Democratic Republic, Cote d'Ivoire, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe	12-36 months	cross sectional	community-based
Mutua et al	2016	Kenya	12-23 months	cohort	community-based
Mutua et al	2020	Kenya	12-23 months	cross sectional	community-based
Mvula et al	2016	Malawi	>6years	cohort	community-based
Nadella et al	2019	Tanzania	0-12months	cross sectional	community-based
Nakatudde et al	2019	Uganda	6-24 months	cross sectional	facility-based
Nalley et al	2019	Nigeria	12-23 months	cross sectional	community-based
Narvaez et al	2017	Colombia	0-6 years	cross sectional	community-based
Ndiritu et al	2006	Kenya	9-23 months	cross sectional	community-based
Ni et al	2017	China	12-72 months	cross sectional	community-based
Noh et al	2019	Pakistan	unclear	cross sectional	community-based
Noh et al	2018	Pakistan	0-23 months	cross sectional	community-based
Ochoa et al	2015	Peru	0-12 months	cohort	facility-based
Odusanya et al	2000	Nigeria	0-12 months	cross sectional	community-based
Odutola et al	2015	Gambia	12-59 months	cross sectional	facility-based
Olademije et al	2020	Nigeria	0-10months	RCT	facility-based
O'leary et al	2016	Ghana	low birthweight	cohort	community-based
Olusanta	2010	Nigeria	0-3 months	cross sectional	facility-based
Oner et al	2012	Turkey	12-23 months	cross sectional	community-based
Ork et al	2019	Cambodia	5-7 years	cross sectional	community-based
Oue`draogo et al	2013	Burkina Faso	0-5 years	cross sectional	community-based
Parameswaran et al	2012	Sri Lanka	12-23 months	cross sectional	community-based
Park et al	2011	South Korea	1-72 months	cross sectional	community-based
Park et al	2013	South Korea	unclear	cross sectional	facility-based

Patel et al	2014	Philippines	0-6 weeks	cross sectional	facility-based
Patel et al	2016	French Polynesia	0-6 years	cross sectional	school-based
Pe`rie`res et al	2021	Senegal	unclear	cross sectional	community-based
Perrinho et al	1987	South Africa	12-23 months	cross sectional	community-based
Pertet et al	2018	Kenya	0-23 months	cross sectional	community-based
Pham et al	2018	Vietnam	6-11 months	cross sectional	community-based
Pindyck et al	2019	Burkina Faso, Ghana, Rwanda, Zimbabwe	3-36 months	cross sectional	community-based
Poorolajal et al	2012	Iran	12-24 months	cross sectional	community-based
Prinja et al	2009	India	0-17 months	cohort	community-based
Quazi et al	2018	Pakistan	0-12months	cross sectional	facility-based
Raguindin et al	2021	Philippines	0-12 months	cross sectional	facility-based
Rainey et al	2012	Haiti	12-23 months	cross sectional	community-based
Ramaswamy et al	2014	India	0-12 months	cross sectional	Facility-based
Rammohan et al	2015	India	12-60 months	cross sectional	community-based
Rammohan et al	2014	India	12-59 months	cross sectional	community-based
Rauniyar et al	2020	Mongolia	12-23 months	cross sectional	community-based
Rejali et al	2015	Iran	24 - 47 months	cross sectional	community-based
Roux et al	2017	South Africa	0-11 months	cohort	community-based
Sadoh et al	2009	Nigeria	>12 months	cross sectional	facility-based
Sadoh et al	2014	Nigeria	2 months - 15 years	cross sectional	facility-based
Sadoh et al	2013	Nigeria	unclear	cross sectional	facility-based
Sahoo et al	2018	India	0-11 months	cross sectional	facility-based
Salameh et al	2021	Jordan	0-18 months	cross sectional	facility-based
Saraiva et al	2015	Brazil	7-18 months	cross sectional	community-based
Sartori et al	2017	Brazil	0-23 months	cohort	HIMS data
Sato	2020	Nigeria	12-59months	cross sectional	community-based
Schoeps et al	2014	Burkina Faso	12-23 months	cross sectional	community-based
Schweitzer et al	2016	Honduras	0-59 months	cross sectional	community-based
Schweitzer et al	2017	Albania, Armenia, Azerbaijan, Bangladesh, Benin, Bolivia, Burkina Faso, Burundi, Cambodia, Cameroon,	12-60 months	cross sectional	community-based

		Colombia, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Egypt, Gabon, Ghana, Guyana, Honduras, Jordan, Kenya, Kyrgyzstan, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mozambique, Namibia, Niger, Nigeria, Pakistan, Peru, Republic of Moldova, Rwanda, Senegal, Sierra Leone, Swaziland, Tajikistan, Tanzania, Timor-Leste, Uganda, Zambia, Zimbabwe			
Schweitzer et al	2015	Armenia, Kyrgyzstan	0-59 months	cross sectional	community-based
Scott et al	2014	Gambia	9-60 months	cross sectional	community-based
Senessie et al	2007	Sierra Leone	0-35 months	cross sectional	community-based
Sheik et al	2018	Bangladesh	12-23 months	cross sectional	community-based
Shrivastwa et al	2016	India	0-60 months	cross sectional	mixed
Siddiqi et al	2010	Pakistan	unclear	cross sectional	community-based
Siddiqi et al	2007	Pakistan	0-11 months	cross sectional	community-based
Siddiqi et al	2020	Pakistan	0-12months	RCT	facility-based
Singh et alz	2020	India	12-23 months	cross sectional	community-based
Soeung et al	2012	Cambodia	unclear	cross sectional	facility-based
Sood et al	2015	India	12-23 months	cross sectional	community-based
Sua`rez-castaneda et al	2014	El Salvador	23-59 months	cross sectional	community-based
Subbish et al	2019	India	0-23 months	cross sectional	facility-based
Sun et al	2010	China	12-35 months	cross sectional	community-based
Tang et al	2017	China	18-54 months	cross sectional	community-based
Tang et al	2021	China	18-48 months	cross sectional	community-based
Tang et al	2016	China	18-54 months	cross sectional	community-based
Tauil et al	2017	Brazil	0-24 months	cohort	facility-based
Thysen et al	2014	Guinea-Bissau	12-23 months	cross sectional	community-based
Tippins et al	2017	Federated States of Micronesia	24-35 months	cross sectional	community-based
Toikilik et al	2010	Papua New Guinea	12-23 months	cross sectional	community-based
Tooke et al	2019	South Africa	low birthweight	cross sectional	HIMS data

Tsega et al	2016	Malawi	12-23 months	cross sectional	community-based
Upadhyah et al	2017	India	low birthweight	RCT	facility-based
Vasudevan et al	2014	Bangladesh	11-18 weeks	RCT	community-based
Vasudevan et al	2020	Tanzania	12-23 months	cross sectional	facility-based
Vonasek et al	2016	Uganda	0-5 years	cross sectional	community-based
Wagner et al	2014	China	8 months - 6 years	cross sectional	community-based
Wagner et al	2019	India	0-5 years	cross sectional	mixed
Wagner et al	2016	China	0-24 months	cross sectional	HIMS data
Wagner et al	2014	China	2-7 years	cohort	HIMS data
Wakadha et al	2013	Kenya	0-14 weeks	RCT	facility-based
Wallace et al	2012	Philippines	5-7 months	cross sectional	facility-based
Wallace et al	2019	Indonesia	0-11months	RCT	facility-based
Wambui et al	2017	Kenya	0-23 months	cross sectional	facility-based
Wang et al	2007	China	1-20 months	RCT	community-based
Waroux et al	2013	Tanzania	0-23 months	cross sectional	community-based
Wiesen et al	2016	Papua New Guinea	0-11 months	cross sectional	mixed
Wu et al	2016	China	0-24 months	cross sectional	community-based
Wu et al	2017	China	6-8 years	cross sectional	community-based
Wu et al	2015	China	1-14 years	cross sectional	community-based
Xiao et al	2012	China	0-14 years	cross sectional	community-based
Yadav et al	2012	India	0-5 years	cross sectional	HIMS data
Yang et al	2021	China	8-83 months	cross sectional	community-based
Yang et al	2019	China	2 -7 years	cross sectional	HIMS data
Zaidi et al	2014	Pakistan	0-5 years	cross sectional	community-based
Zhou et al	2016	China	unclear	cross sectional	facility-based
Zhou et al	2009	China	unclear	cross sectional	community-based
Zivich et al	2017	Democratic Republic of the Congo	0-6 months	cohort	facility-based

Appendix 4: Chapter 3 (Research Paper PRISMA-ScR Checklist)

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

Title: Timeliness of routine childhood vaccination in 103 low-and middle-income countries: a scoping review to map methodological and measurement gaps, 1978 – 2021

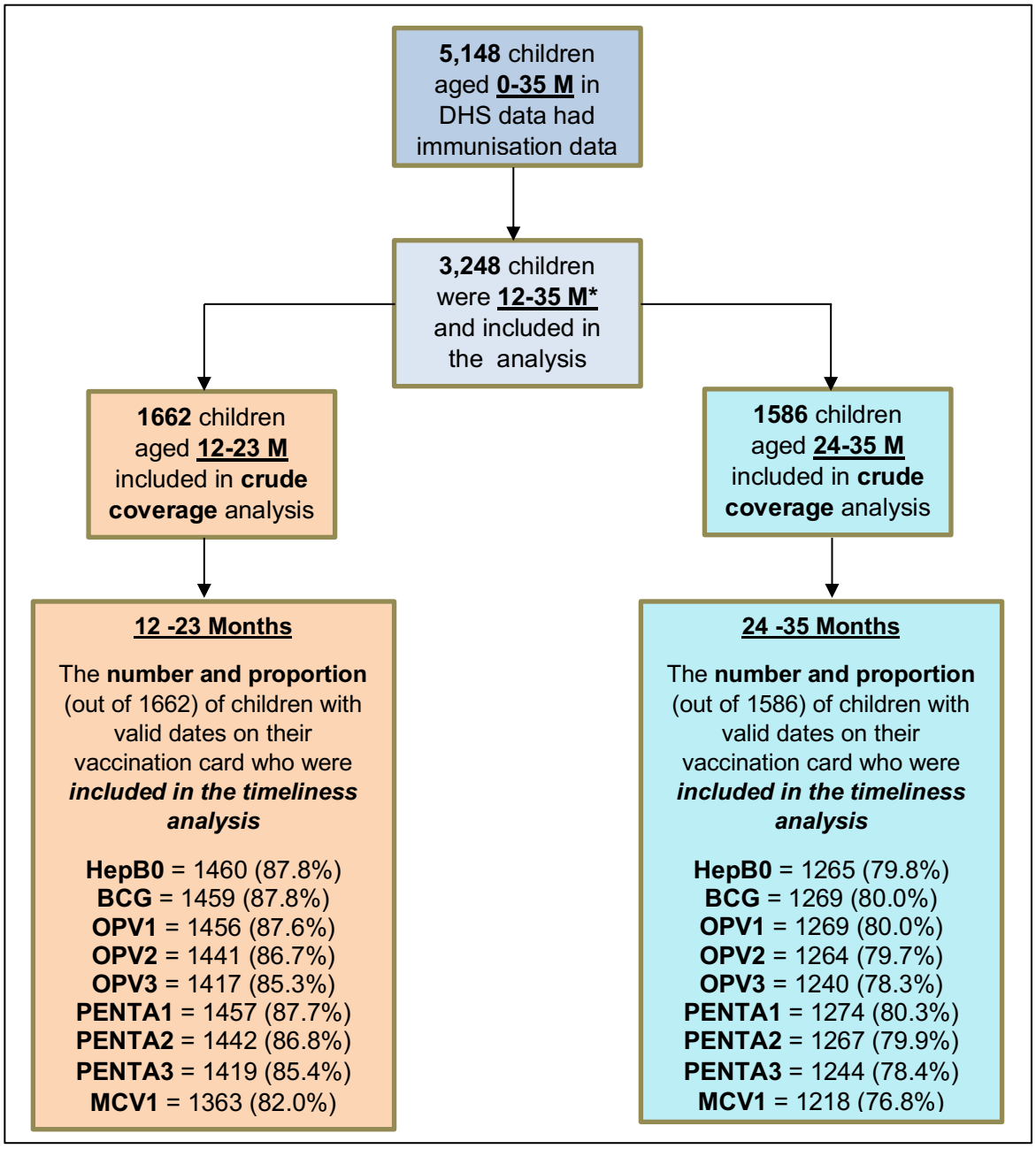
SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Page 4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Page 4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Page 5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Page 5-6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page 5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Page 5, and appendix
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Page 6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Page 6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Not done because not explicitly required for a scoping review
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Page 7
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Page 7
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Page 7
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not done because not explicitly required for a scoping review
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Not applicable as this is a protocol
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Page 8 - 10
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Page 11 - 12
Limitations	20	Discuss the limitations of the scoping review process.	Page 13
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Page 13
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Page 7, and 14

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

Appendix 5: Chapter 4 (Research Paper 1 S1 Figure)

S1 Figure: Flowchart displaying children included in this study by age group and birth/vaccination data completeness from the Gambia DHS 2019-2020 for computing timeliness.



***Note:** This analysis was restricted to the 12-35 months age group to ensure that the timeliness estimates is comparable to the crude vaccination coverage rates which are published by the DHS survey.

Appendix 6: Chapter 4 (Research Paper 1 S1 Table)

S1 Table: Median number of days children were vaccinated too early and interquartile ranges for all vaccines for children 12-23 and 24-35 months in The Gambia

	12 - 23 Months			24 - 35 Months		
Vaccines	**Median**	**1st quartile**	**3rd quartile**	**Median**	**1st quartile**	**3rd quartile**
OPV1	7	2	17	8	2	18
OPV2	3	2	12	5	2	13.5
OPV3	4	2.3	12	5.5	3	13.5
PENTA1	6	2	15.8	8	2	17
PENTA2	3	1	11	4.5	2	13.8
PENTA3	4	2	10	5	3	13
MCV1	14.5	6.8	26.3	9	4	26

Note: Pentavalent vaccine (DPT-HepB-Hib); OPV = Oral Polio Vaccine; MCV = Measles Containing Vaccine

Appendix 7: Chapter 4 (Research Paper 1 S2 Table)

S2 Table: Median delays and interquartile ranges for all vaccines for children 12-23 and 24-35 months in The Gambia

	12 - 23 Months			24 - 35 Months		
Vaccine	Median	1st quartile	3rd quartile	Median	1st quartile	3rd quartile
HepB0	16	9	26	17	10	28
BCG	11	5	19.5	13	6	21
OPV1	14	5	26	11	4	29
OPV2	20	8	35.3	22	9	45
OPV3	26	11	52	28	11	57
PENTA1	15	5	26.5	12	4	30
PENTA2	21	8	37	22	9	45
PENTA3	26	11	51	27	11	55
MCV1	20	8	42	22	9	48.8

Note: HepB0 = Birth dose of Hepatitis B vaccine; BCG = Bacille Calmette-Guérin; PENTA = Pentavalent vaccine (DPT-HepB-Hib); OPV = Oral Polio Vaccine; MCV = Measles Containing Vaccine

Appendix 8: Chapter 4 (Research Paper 2 Supplementary material)

Mapping the timeliness of routine vaccination among 12-35 months old children in The Gambia: a spatial modelling study

Oghenebrume Wariri, Chigozie Edson Utazi, Uduak Okomo, C. Jessica E. Metcalf, Malick Sogur, Sidat Fofanna, Kris A Murray, Chris Grundy, Beate Kampmann

Additional information on covariate data processing

Table S1: Geospatial covariate layers (The Gambia) included in the modelling process after the covariate selection process

Vaccine	Modelled outcome	Selected covariate from the selection process**	Year(s)	Type
HepB0	Delayed	Distance to edge of cultivated areas	2015	Continuous
		Digital elevation model	2001	Continuous
		Pigs density	2018	Continuous
		Average number of wet days	2016-19	Continuous
		Proximity to national borders	2017	Continuous
		Average potential evapotranspiration	2016-19	Continuous
PENTA3	Delayed	Digital elevation model	2001	Continuous
		Average number of wet days	2016-19	Continuous
		Proximity to national borders	2017	Continuous
		Average MODIS NDVI	2016-19	Continuous
		Average MODIS night time land surface temperature	2016-19	Continuous
		Average potential evapotranspiration	2016-19	Continuous
	Timely	Distance to settlement/built-up areas	2014	Continuous
		Average precipitation	2016-19	Continuous
		Average MODIS EVI	2016-19	Continuous
		Average MODIS night time land surface temperature	2016-19	Continuous
		Average maximum temperature	2016-19	Continuous
		Average potential evapotranspiration	2016-19	Continuous
MCV1	Delayed	Average number of wet days	2016-19	Continuous
		Average MODIS night time land surface temperature	2016-19	Continuous
		Average potential evapotranspiration	2016-19	Continuous
	Timely	Average number of wet days	2016-19	Continuous
		Proximity to national borders	2017	Continuous
		Average MODIS night time land surface temperature	2016-19	Continuous
		Average potential evapotranspiration	2016-19	Continuous

Note: HepB0 = Birth dose of Hepatitis B vaccine; **PENTA3** = third dose of pentavalent vaccine; **MCV1** = first dose of the measles containing vaccine; **EVI** = Enhanced vegetation index; **NVDI** = Normalized Difference Vegetation Index (used to quantify vegetation greenness and is useful in understanding vegetation density). Urbanicity (a categorical measure showing if a location was urban or rural) was included as a covariate for all modelled outcomes even if it was not chosen during the covariate selection process, as a way of accounting for the urban/rural stratification used in the survey design. Covariate surfaces and relevant population estimates corresponding to the survey years for children one year and below in The Gambia were downloaded from WorldPop (www.worldpop.org) (see reference at the end of the document).[1]
**To avoid the problem of circularity in our analyses (i.e., using the same data twice), we decided to exclude spatial access to facilities as a covariate surface from the current analysis. This is because, we plan further analysis using geographic access to facilities to estimate numbers of children within different travel time bands who had delayed or untimely vaccination.

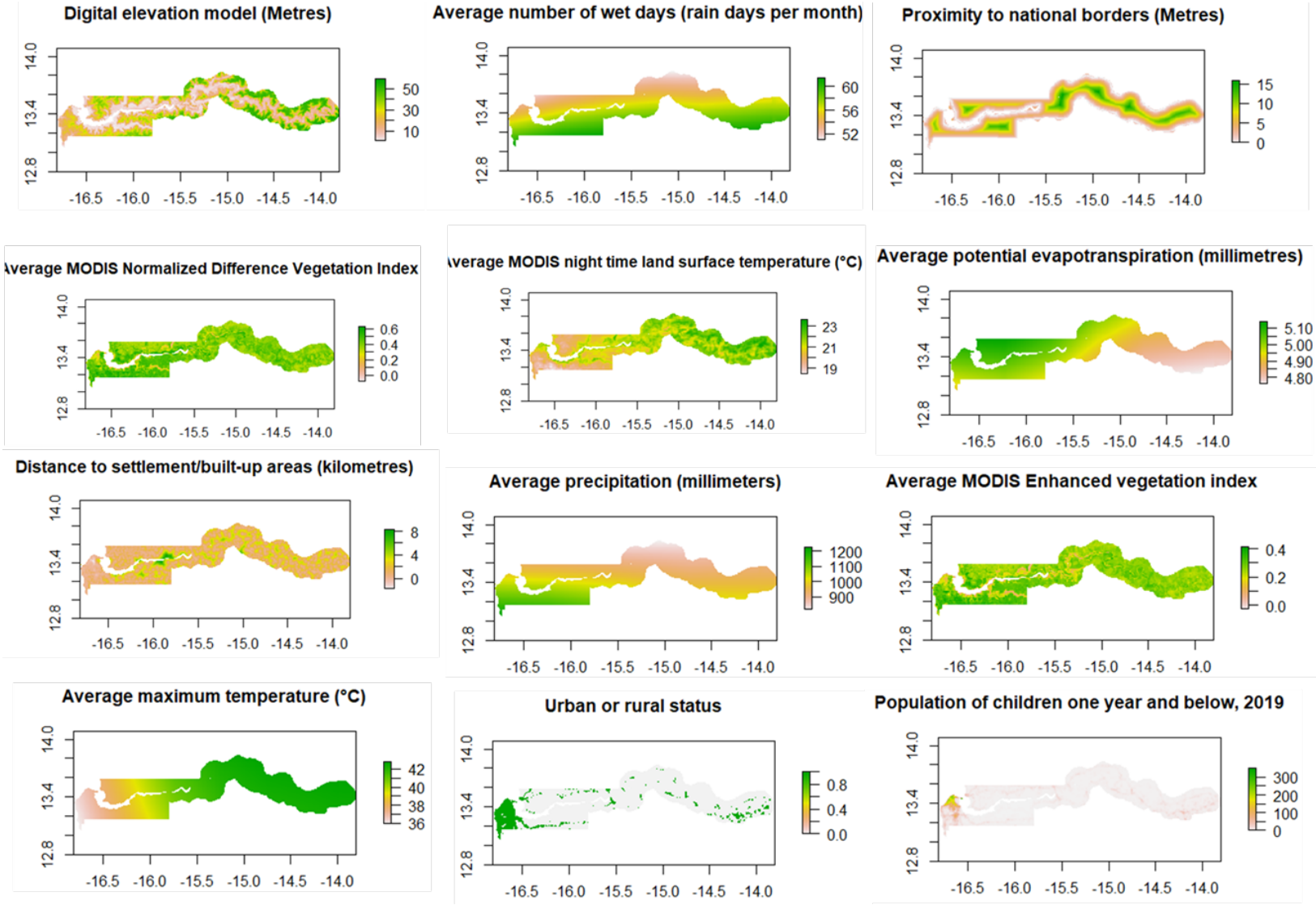


Figure S1: Plots of all the geospatial covariate layers (1 x 1 km) included after the covariate selection process and used for the modelling of delayed and timely HepB0, PENTA3 and MCV1

Additional information on variogram analysis

The observed HepB0, PENTA3 and MCV1 timeliness (i.e., timely, delayed, and early vaccination) at the cluster level generally exhibit spatial correlation, as evidenced by the fact that clusters in close proximity tend to have similar observed prevalence of delayed, early, or timely vaccination. However, it is worth noting that there are instances where clusters that are geographically close to each other display substantial differences in observed timeliness. These discrepancies may be attributable to factors other than spatial location and/or sampling variation, such as outcome variation.

The variogram is a standard tool for examining spatial dependence. To evaluate the need for accounting for spatial autocorrelation when modelling the indicators (i.e., delayed HepB0, delayed PENTA3, delayed MCV1, timely PENTA3 and timely MCV1), we fitted binomial regression models with independent and identically distributed (iid) random effects. Using the estimates of the iid random effect, we fitted a variogram (figure S2) in each case to assess the presence of residual spatial autocorrelation in the models. The semi-variogram (Figure S2) shows an increasing trend with increasing distance between points, that flattens out at a range of around 60 km(HepB0), 100 km (PENTA3) and 80 km (MCV1), indicating that locations farther apart than that distance are not spatially correlated.

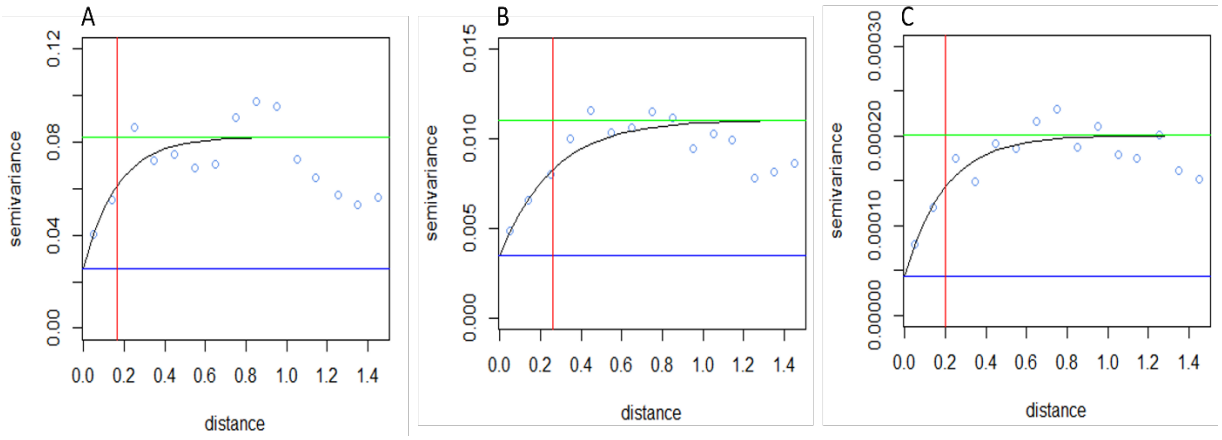


Figure S2: **(A)** The empirical semi-variogram for the prevalence of delayed **HepB0** based on estimates of the iid random effect in the non-spatial binomial mixed model; **(B)** The empirical semi-variogram for the prevalence of delayed **PENTA3** based on estimates of the iid random effect in the non-spatial binomial mixed model; **(C)** The empirical semi-variogram for the prevalence of delayed **MCV1** based on estimates of the iid random effect in the non-spatial binomial mixed model.

Note: Where the ***blue line*** meets the y-axis indicates the ***nugget*** (typically associated with "measurement error" and small scale variation), while where the ***green line*** meets the semi-variance curve is the ***range***. *Nuggets* suggest the presence of additional variation in the cluster-level outcome beyond the variation accounted for by covariates and the spatial field, indicating the existence of non-spatial excess variation.

Additional information on the spatial model fitting

The general model we used to create 1x1 km prevalence maps of the timeliness indicators is a geostatistical model with a binomial likelihood. Let $s_i, i = 1, \ldots, n$ denote the survey cluster locations, where n is the number of clusters; $Y(s_i)$ – the number of children who had early, timely or delayed vaccination for a given vaccine dose at the survey location s_i and $m(s_i)$ – the number of children sampled from the location. The model can be written as:

$$Y(s_i)|p(s_i) \sim \text{Binomial}\big(m(s_i), p(s_i)\big),$$
$$\text{logit}(p(s_i)) = \text{x}(s_i)^T\beta + \omega(s_i) + \epsilon(s_i), \quad (1)$$

where $p(s_i)$ $(0 \leq p(s_i) \leq 1)$ is the true prevalence at location s_i, $\text{x}(s_i)$ is a vector of covariate data associated with s_i, β is a vector of the corresponding regression coefficients, $\epsilon(s_i)$ is an independent and identically distributed (iid) Gaussian random effect with variance, σ_ϵ^2, used to model non-spatial residual variation, and $\omega(s_i)$ is a Gaussian spatial random effect used to capture residual spatial correlation in the model. To model $\omega = (\omega(s_1), \ldots, \omega(s_n))^T \sim N(0, \Sigma_\omega)$, we assume that Σ_ω follows the Matérn covariance function[2] given by $\Sigma_\omega(s_i, s_j) = \frac{\sigma^2}{2^{\nu-1}\Gamma(\nu)}\big(\kappa \parallel s_i - s_j \parallel\big)^\nu K_\nu(\kappa \parallel s_i - s_j \parallel)$, where $\|.\|$ denotes the Euclidean distance between cluster locations s_i and s_j, $\sigma^2 > 0$ is the marginal variance of the spatial process, κ is a scaling parameter related to the range $r(r = \frac{\sqrt{8\nu}}{\kappa})$ – the distance at which spatial correlation is close to 0.1, and K_ν is the modified Bessel function of the second kind and order $\nu > 0$. Further, for identifiability reasons, we set the smoothing parameter, $\nu = 1$, see Lindgren et al.[3]

We adopted a fully Bayesian approach to fit model (1) for each modelled timeliness indicator. We assigned a $N(0,10^3 I)$ prior to the regression parameter β. Following Simpson et al,[4] we also placed a penalized complexity (PC) prior on σ_ϵ such that $p(\sigma_\epsilon > 3) = 0.01$. Similarly, a joint PC prior was placed on the covariance parameters of the spatial random effect, ω following the approach by Fuglstad et al.[5] These were: $p(r < r_0) = 0.01$ and $p(\sigma > 3) = 0.01$, with r_0 chosen to be the 5% of the extent of The Gambia in the east-west direction. The model was implemented using the integrated nested Laplace approximation—stochastic partial differential equation (INLA-SPDE) approach.[6] The INLA approach is a faster alternative to the traditional MCMC technique for performing approximate Bayesian inference. The approach uses numerical techniques to approximate the marginal posterior distributions of each of the unknown quantities in the model. The SPDE approach facilitates the estimation of the Gaussian spatial random effect, ω, by reducing the computational burden involved in the estimation of Σ_ω through a Gaussian Markov random field (GMRF) representation.[6] Further details on the implementation of the INLA-SPDE approach are provided in Utazi et al.[7,8]

To ensure that the modelled prevalence estimates for the indicators of timeliness were consistent for each vaccine dose, i. e. $p(\text{early vaccination}) + p(\text{timely vaccination}) + p(\text{delayed vaccination}) = 1$ for each prediction location, we modelled $p(\text{timely vaccination})$ and $p(\text{delayed vaccination})$ independently using (1) and then derived $p(\text{early vaccination})$ as $1 - p(\text{timely vaccination}) - p(\text{delayed vaccination})$ from these using the corresponding posterior samples. Wherever necessary, the modelled estimates were adjusted to ensure that all the indicators were consistent for each vaccine dose and prediction location. The decision to model $p(\text{timely vaccination})$ and $p(\text{delayed vaccination})$ was because there were more observed cases of both events for both vaccine doses relative to early vaccination. Hence, both timeliness indicators were more likely to be better explained by the covariates used in the analysis. Using the 1×1 km predictions from model (1), we obtained modelled estimates at the ward, (ADM3), district (ADM2) and regional (ADM1) levels as population-weighted averages taken over all the grid cells falling within each administrative area. Further, we compared the regional level estimates with design-based direct

survey estimates computed using the survey package[9] to further validate the fitted models. All the analyses were carried out in R (R Development Core Team, 2023) using the R-INLA package.[10]

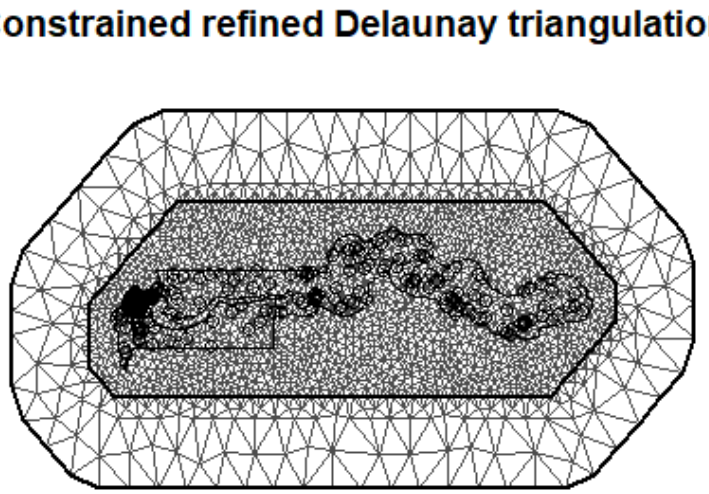


Figure S3: An example of fine triangulation mesh for modelled delayed MCV1 in The Gambia.

Model validation metrics

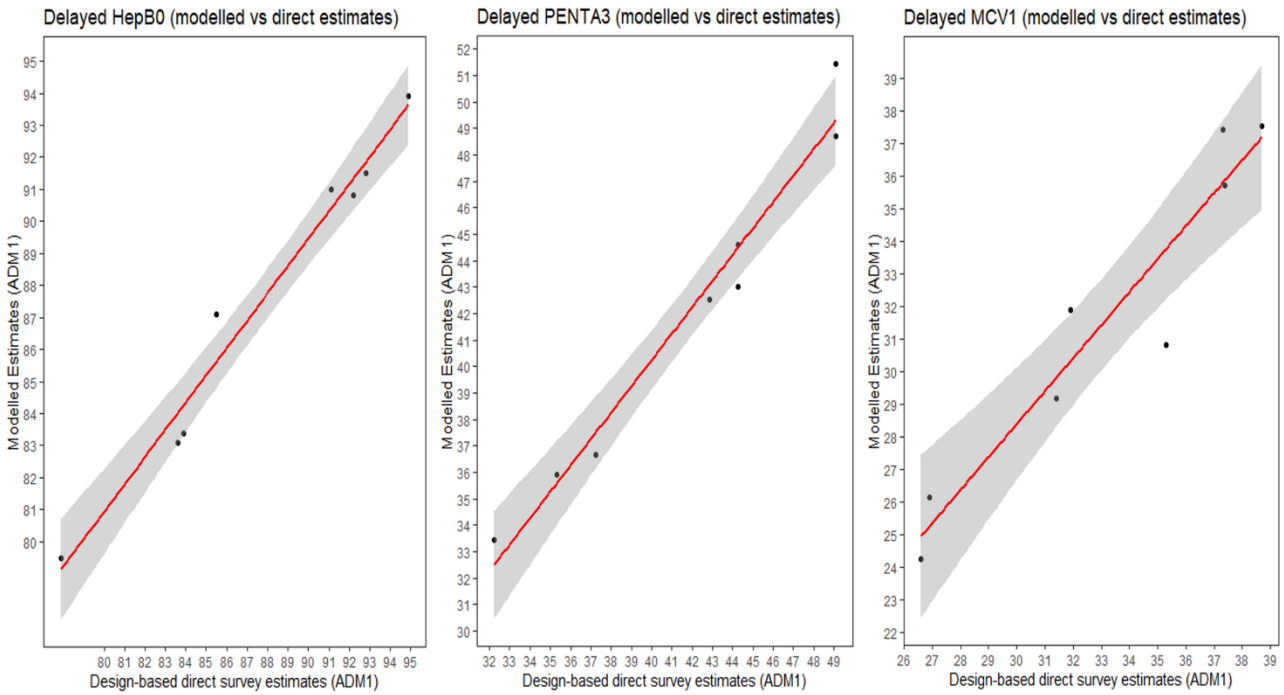


Figure S4: Validation plot showing comparison of modelled estimates (delayed PENTA3/MCV1) and designed-based direct survey estimates at the first administrative level (Local Government Areas) for children aged 12-35 months in The Gambia.

Note: The designed based direct survey estimates (The Gambia 2019-2020 Demographic and Health Survey) are representative at the national, and at the Local Government Area levels (i.e., ADM1).

Table S2: Summary district-level model validation statistics based on 5-fold cross-validation approach for the modelled vaccine outcomes

Vaccine	Outcome*	Bias	MAE	RMSE
HepB0	Delayed	-0.003	0.06	0.04
PENTA3	Delayed	-0.004	0.03	0.05
	Timely	-0.006	0.04	0.05
MCV1	Delayed	-0.003	0.02	0.02
	Timely	-0.002	0.03	0.04

* We chose to model delayed HepB0, delayed/timely PENTA3 and delayed/timely MCV1 due to the higher number of observed cases for these events in comparison to timely HepB0 or early PENTA3/MCV1. **MAE** = Mean absolute error; **RMSE** = root mean squared error.

Additional tables and maps related to the objectives of the study

Table S3: Districts and wards with the highest (>90%) modelled prevalence of delayed birth dose of hepatitis B vaccine **(HepB0)** and their accompanying credible interval width

Region	LGA	District	Ward	Prevalence	95% CI width
Central River	Janjanbureh	Lower Fuladu West	Kerewan	95.6	2.3
Upper River	Basse	Basse	Sabi	95.6	3.0
Upper River	Basse	Jimara	Gambissara	95.2	2.4
Central River	Kuntaur	Upper Saloum	Panchang	95.2	2.6
Upper River	Basse	Tumana	Dampha Kunda	94.8	2.3
Central River	Janjanbureh	Niamina East	Jarreng	94.7	3.0
Upper River	Basse	Basse	Basse	94.7	2.2
Upper River	Basse	Wuli West	Sutukonding	94.4	3.2
Central River	Janjanbureh	Lower Fuladu West	Fulabantang	94.3	2.9
Central River	Janjanbureh	Janjanbureh	MacCarthy	94.2	3.4
Central River	Janjanbureh	Lower Fuladu West	Brikamaba	94.1	3.0
Upper River	Basse	Tumana	Kularr	94.0	2.5
Upper River	Basse	Wuli East	Baja Kunda	93.8	3.0
Upper River	Basse	Jimara	Julangel	93.8	3.1
Upper River	Basse	Wuli West	Sare Ngai	93.8	3.4
Upper River	Basse	Sandu	Diabugu	93.3	3.6
Upper River	Basse	Sandu	Misera	93.3	3.7
Upper River	Basse	Kantora	Garawol	93.2	3.0
Upper River	Basse	Kantora	Koina	93.1	3.1
Central River	Kuntaur	Upper Saloum	Njaw	93.1	2.8
Central River	Kuntaur	Sami	Pachonki	92.7	3.5
Banjul	Banjul	Banjul Central	New Town West	92.2	3.5
Central River	Janjanbureh	Niamina West	Katamina	92.1	4.3
West Coast	Brikama	Kombo South	Gunjur	91.8	4.7
Central River	Kuntaur	Sami	Banni	91.7	3.3
North Bank	Kerewan	Sabach - Sanjal	Sabach	91.7	3.9
Central River	Kuntaur	Niani	Nyanga	91.7	4.1
Central River	Kuntaur	Nianija	Chamen	91.5	3.7
Lower River	Mansa konko	Jarra East	Pakaliba	91.5	4.8
Central River	Janjanbureh	Niamina East	Kudang	91.4	3.6
Central River	Kuntaur	Lower Saloum	Ballangharr	91.1	5.0

Note: Delayed HepB0 vaccination ranged from 63.5% to 95.6% at the ward level (ADM3). This table only reflect wards (including the districted they are situated) with the highest modelled prevalence (i.e., >90%) of delayed HepB0. **CI** = Credible Interval.

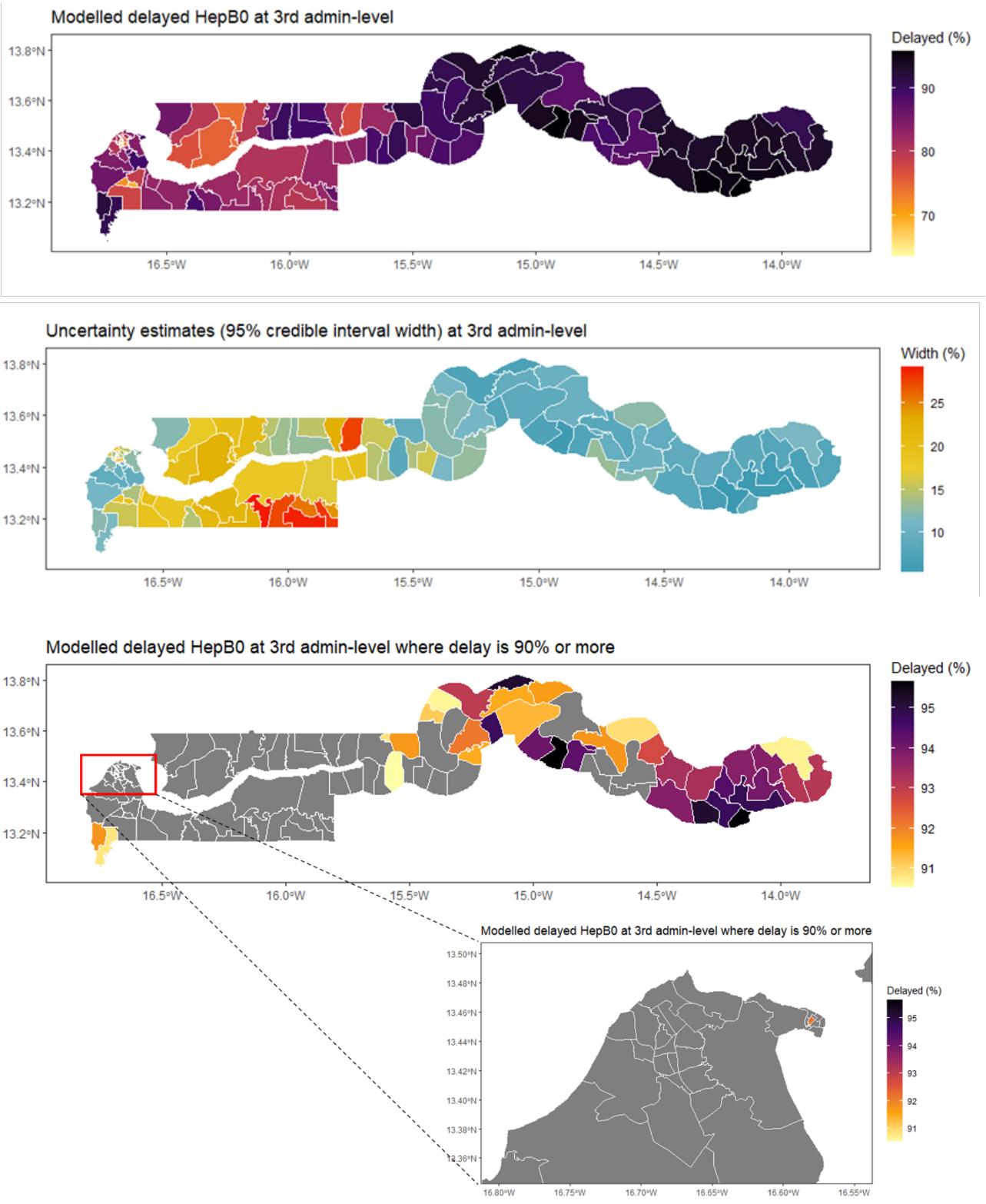


Figure S5: The map illustrates the predicted prevalence of delayed birth dose of hepatitis B vaccine (HepB0) at the ward level and accompanying uncertainty estimate. It also highlights the wards with the highest modelled prevalence, surpassing 90%, of delayed HepB0.

Table S4: Districts and wards with the highest (>45%) modelled prevalence of delayed third dose of pentavalent vaccine **(PENTA3)** and their accompanying credible interval width

Region	LGA	District	Ward	Prevalence	95% CI width
Upper River	Basse	Basse	Sabi	54.5	14.4
Banjul	Banjul	Banjul South	Portugiese Town	54.1	29.7
Upper River	Basse	Tumana	Kularr	53.9	9.8
Upper River	Basse	Jimara	Julangel	52.6	10.8
Upper River	Basse	Tumana	Dampha Kunda	52.2	10.0
Central River	Janjanbureh	Janjanbureh	MacCarthy	52.2	15.5
Central River	Janjanbureh	Upper Fuladu West	Sare Soffie	52.1	12.6
Upper River	Basse	Kantora	Garawol	51.7	11.4
Central River	Janjanbureh	Upper Fuladu West	Bansang	51.0	11.4
Upper River	Basse	Jimara	Gambissara	50.7	11.6
Central River	Janjanbureh	Niamina East	Jarreng	50.5	12.7
West Coast	Brikama	Kombo South	Karthong	50.4	15.4
Upper River	Basse	Kantora	Koina	50.3	12.2
Upper River	Basse	Basse	Basse	50.3	10.9
Central River	Janjanbureh	Lower Fuladu West	Fulabantang	49.9	10.2
Upper River	Basse	Sandu	Diabugu	49.6	10.1
Central River	Janjanbureh	Lower Fuladu West	Kerewan	49.2	11.1
Central River	Janjanbureh	Upper Fuladu West	Daru	49.0	13.0
West Coast	Brikama	Kombo South	Gunjur	48.5	14.7
West Coast	Brikama	Kombo Central	Marakissa	48.5	12.6
West Coast	Brikama	Kombo South	Sanyang	48.4	11.5
West Coast	Brikama	Kombo East	Giboro	48.3	14.2
Central River	Kuntaur	Sami	Pachonki	47.7	12.1
Central River	Kuntaur	Sami	Banni	46.0	10.2
Upper River	Basse	Wuli East	Foday Kunda	45.7	11.0
Upper River	Basse	Wuli West	Sutukonding	45.5	11.7
Central River	Kuntaur	Upper Saloum	Panchang	45.5	12.5

Note: Delayed PENTA3 vaccination ranged from 24.2% to 54.5% at the ward level (ADM3). This table only reflect wards (including the districted they are situated) with the highest modelled prevalence (i.e., >45%) of delayed PENTA3. **CI** = Credible Interval.

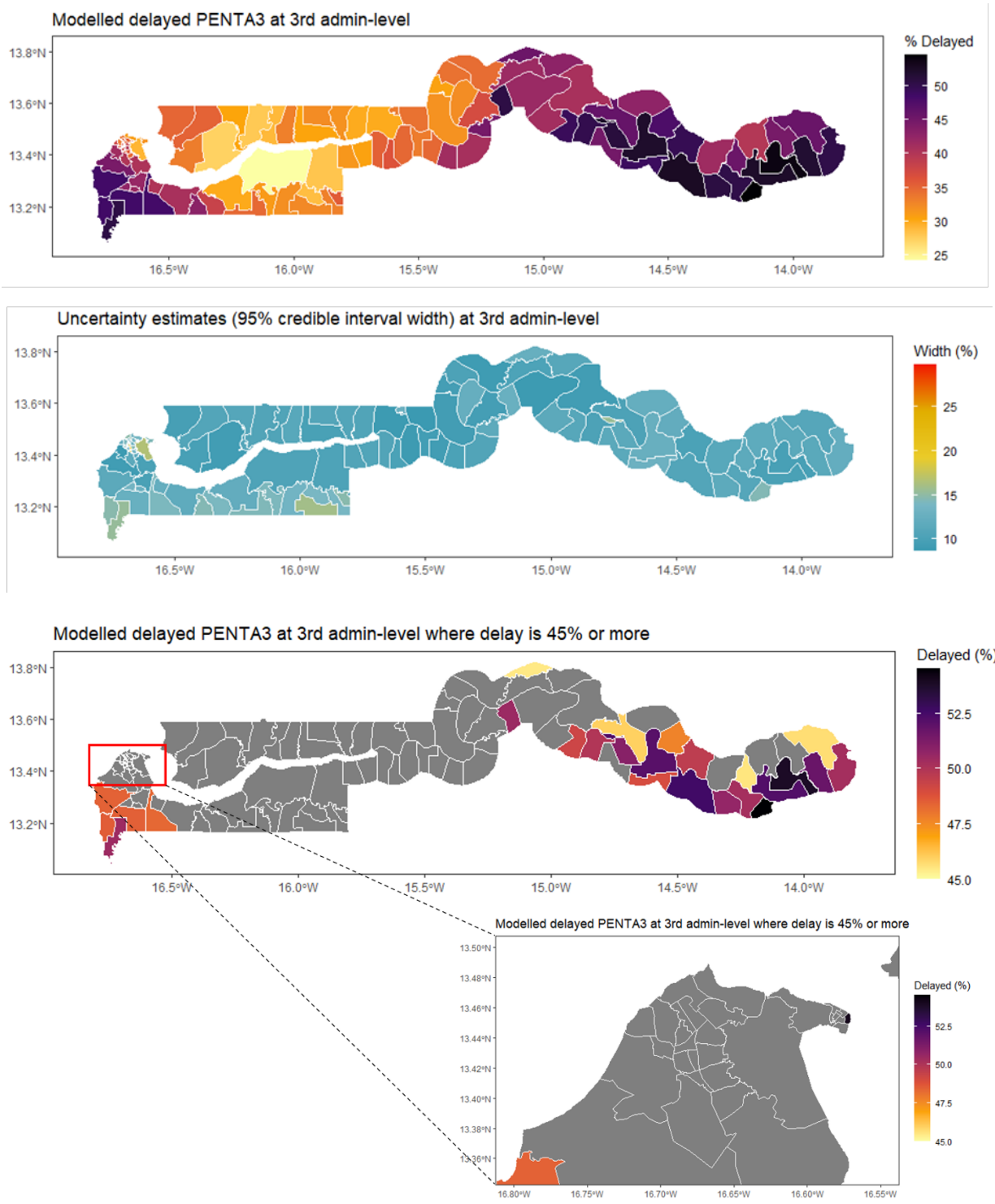


Figure S6: The map illustrates the predicted prevalence of delayed third-dose of the pentavalent vaccine **(PENTA3)** at the ward level and accompanying uncertainty estimate. It also highlights the wards with the highest modelled prevalence, surpassing 45%, of delayed PENTA3.

Table S5: Districts and wards with the highest (>35%) modelled prevalence of delayed first dose of measles containing vaccine **(MCV1)** and their accompanying credible interval width

Region	LGA	District	Ward	Prevalence	95% CI Width
Central River	Janjanbureh	Janjanbureh	MacCarthy	40.2	14.1
Central River	Janjanbureh	Lower Fuladu West	Fulabantang	40.0	10.3
Central River	Kuntaur	Sami	Pachonki	39.8	13.1
Central River	Kuntaur	Sami	Karantaba	39.3	14.6
Central River	Janjanbureh	Upper Fuladu West	Sare Soffie	39.2	9.6
Central River	Janjanbureh	Niamina East	Jarreng	39.0	11.3
Central River	Janjanbureh	Upper Fuladu West	Bansang	38.9	10.3
Upper River	Basse	Jimara	Julangel	38.8	11.3
Upper River	Basse	Tumana	Kularr	38.7	9.9
Central River	Kuntaur	Sami	Banni	38.7	9.7
Central River	Janjanbureh	Lower Fuladu West	Kerewan	38.7	10.6
Upper River	Basse	Sandu	Diabugu	38.3	10.3
Upper River	Basse	Tumana	Dampha Kunda	37.9	9.6
Upper River	Basse	Jimara	Gambissara	37.8	10.5
Upper River	Basse	Basse	Sabi	37.8	12.8
Upper River	Basse	Kantora	Koina	37.7	11.4
Upper River	Basse	Kantora	Garawol	37.4	10.3
Upper River	Basse	Wuli West	Sutukonding	37.2	9.6
Upper River	Basse	Wuli East	Foday Kunda	37.2	10.8
Central River	Janjanbureh	Niamina East	Kudang	37.1	8.9
Upper River	Basse	Basse	Basse	37.1	9.9
Central River	Janjanbureh	Upper Fuladu West	Galleh	36.6	11.0
Central River	Kuntaur	Niani	Kuntaur	36.4	9.2
Central River	Kuntaur	Nianija	Chamen	36.4	10.0
Central River	Kuntaur	Upper Saloum	Panchang	36.3	12.6
Central River	Janjanbureh	Upper Fuladu West	Daru	36.3	12.0
Central River	Kuntaur	Niani	Nyanga	36.2	12.5
Upper River	Basse	Sandu	Misera	36.0	11.1
West Coast	Brikama	Kombo East	Giboro	35.9	13.6
Upper River	Basse	Wuli West	Sare Ngai	35.9	9.7
West Coast	Brikama	Kombo South	Sanyang	35.8	12.3
Upper River	Basse	Wuli East	Baja Kunda	35.4	9.5
West Coast	Brikama	Kombo Central	Marakissa	35.2	11.7
Central River	Janjanbureh	Lower Fuladu West	Brikamaba	35.2	10.3

Note: Delayed MCV1 vaccination ranged from 22.7% to 40.2% at the ward level (ADM3). This table only reflect wards (including the districted they are situated) with the highest modelled prevalence (i.e., >35%) of delayed MCV1. **CI** = Credible Interval.

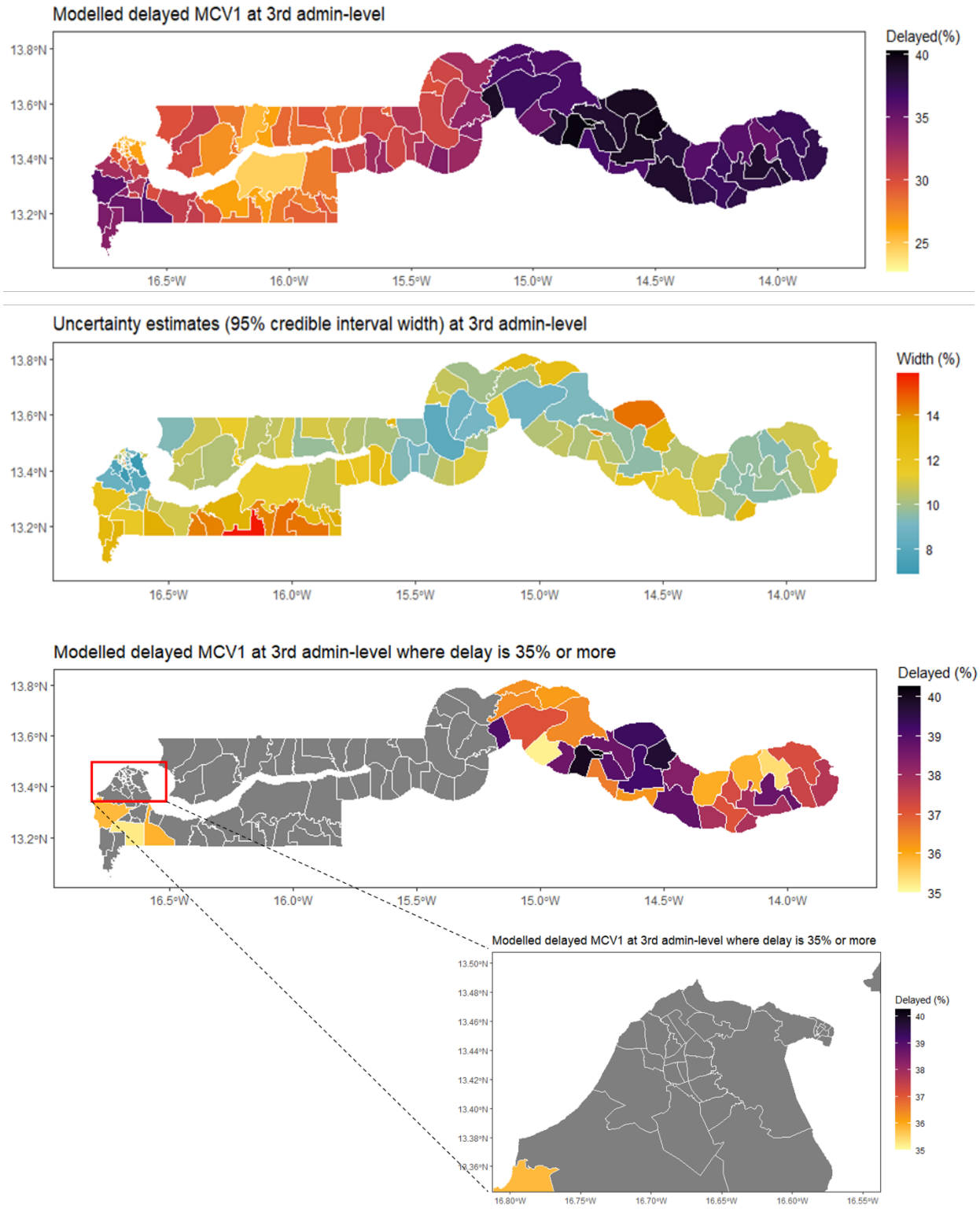


Figure S7: The map illustrates the predicted prevalence of delayed first dose of measles containing vaccine **(MCV1)** at the ward level and accompanying uncertainty estimate. It also highlights the wards with the highest modelled prevalence, surpassing 35%, of delayed MCV1.

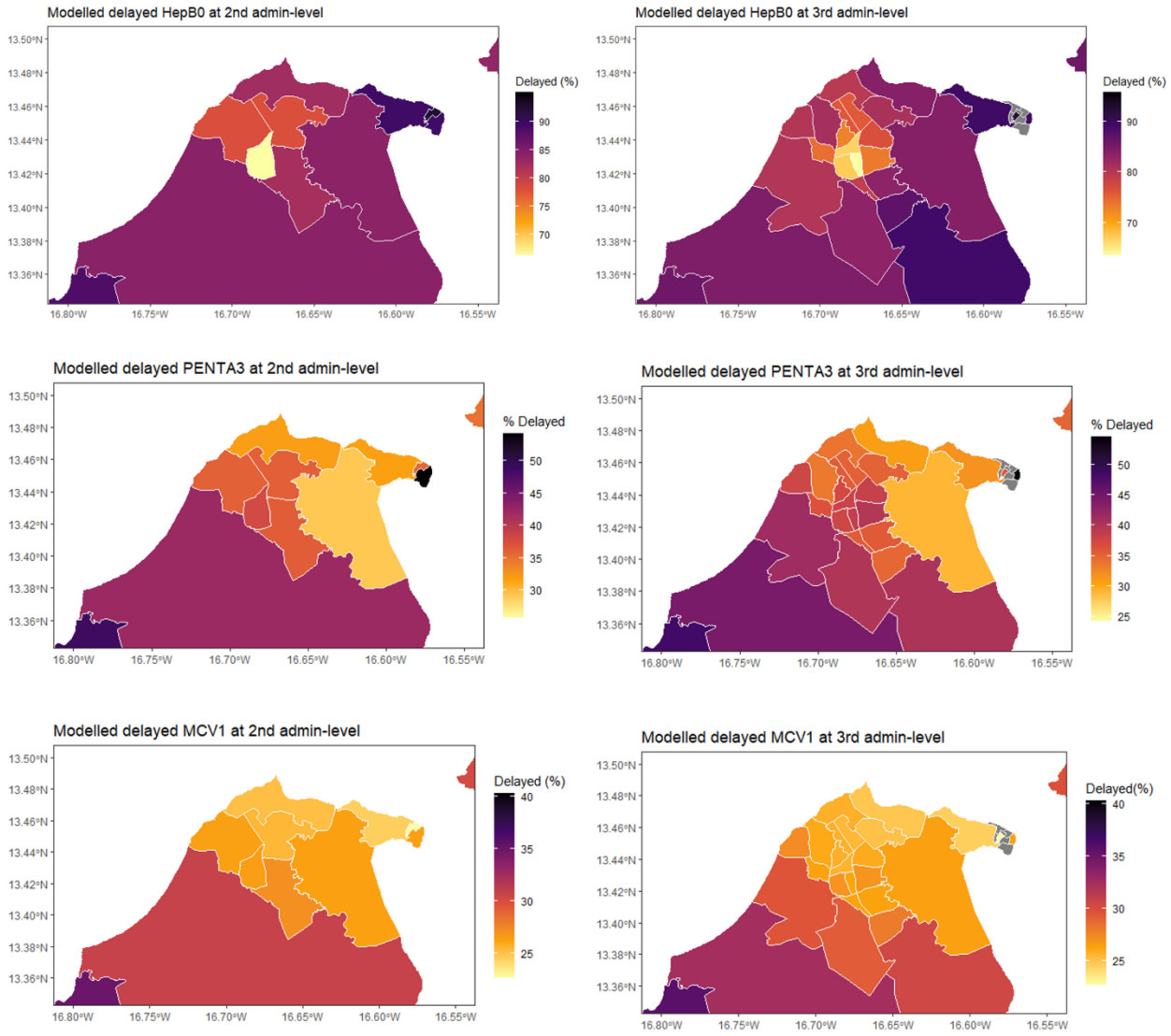


Figure S8: Zoomed in map of districts and wards in the Greater Banjul Area (Banjul and Kanifing LGA) showing the modelled prevalence of delayed HepB0 (top row), PENTA3 (middle row) and prevalence of delayed MCV1 (bottom row)

Table S6: Districts and Wards with Spatial Overlap of High Prevalence of Delayed Vaccination and Substantial Estimated Population of Affected Infants in The Gambia.

Vaccine	Region	LGA	Districts	Wards
HepB0	Upper River	Basse	Kantora	Koina
	Upper River	Basse	Kantora	Garawol
	Upper River	Basse	Tumana	Kularr
	Upper River	Basse	Tumana	Dampha Kunda
	Upper River	Basse	Basse	Sabi
	Upper River	Basse	Basse	Basse
	Upper River	Basse	Jimara	Gambissara
	Upper River	Basse	Jimara	Julangel
	Upper River	Basse	Wuli East	Foday Kunda
	Upper River	Basse	Wuli West	Sare Ngai
	Upper River	Basse	Sandu	Diabugu
	Central River	Janjanbureh	Niamina East	Kudang
	West Coast	Brikama	Kombo South	Gunjur
	West Coast	Brikama	Kombo South	Karthong
PENTA3	Upper River	Basse	Kantora	Koina
	Upper River	Basse	Kantora	Garawol
	Upper River	Basse	Tumana	Kularr
	Upper River	Basse	Tumana	Dampha Kunda
	Upper River	Basse	Basse	Sabi
	Upper River	Basse	Basse	Basse
	Upper River	Basse	Jimara	Gambissara
	Upper River	Basse	Jimara	Julangel
	Upper River	Basse	Wuli East	Foday Kunda
	Upper River	Basse	Sandu	Diabugu
	Central River	Kuntaur	Sami	Banni
	Central River	Kuntaur	Niani	Kuntaur
	Central River	Janjanbureh	Upper Fuladu West	Sare Soffie
	Central River	Janjanbureh	Upper Fuladu West	Bansang
	Central River	Janjanbureh	Niamina East	Kudang
	West Coast	Brikama	Kombo East	Giboro
	West Coast	Brikama	Kombo Central	Marakissa
	West Coast	Brikama	Kombo South	Gunjur
MCV1	Upper River	Basse	Kantora	Koina
	Upper River	Basse	Kantora	Garawol
	Upper River	Basse	Tumana	Kularr
	Upper River	Basse	Tumana	Dampha Kunda
	Upper River	Basse	Basse	Sabi
	Upper River	Basse	Basse	Basse
	Upper River	Basse	Jimara	Gambissara
	Upper River	Basse	Jimara	Julangel
	Upper River	Basse	Wuli East	Foday Kunda
	Upper River	Basse	Sandu	Diabugu
	Central River	Kuntaur	Sami	Banni
	Central River	Kuntaur	Niani	Kuntaur
	Central River	Janjanbureh	Upper Fuladu West	Sare Soffie
	Central River	Janjanbureh	Upper Fuladu West	Bansang
	Central River	Janjanbureh	Niamina East	Kudang
	West Coast	Brikama	Kombo East	Giboro
	West Coast	Brikama	Kombo Central	Marakissa
	West Coast	Brikama	Kombo South	Gunjur
	West Coast	Brikama	Kombo South	Sanyang

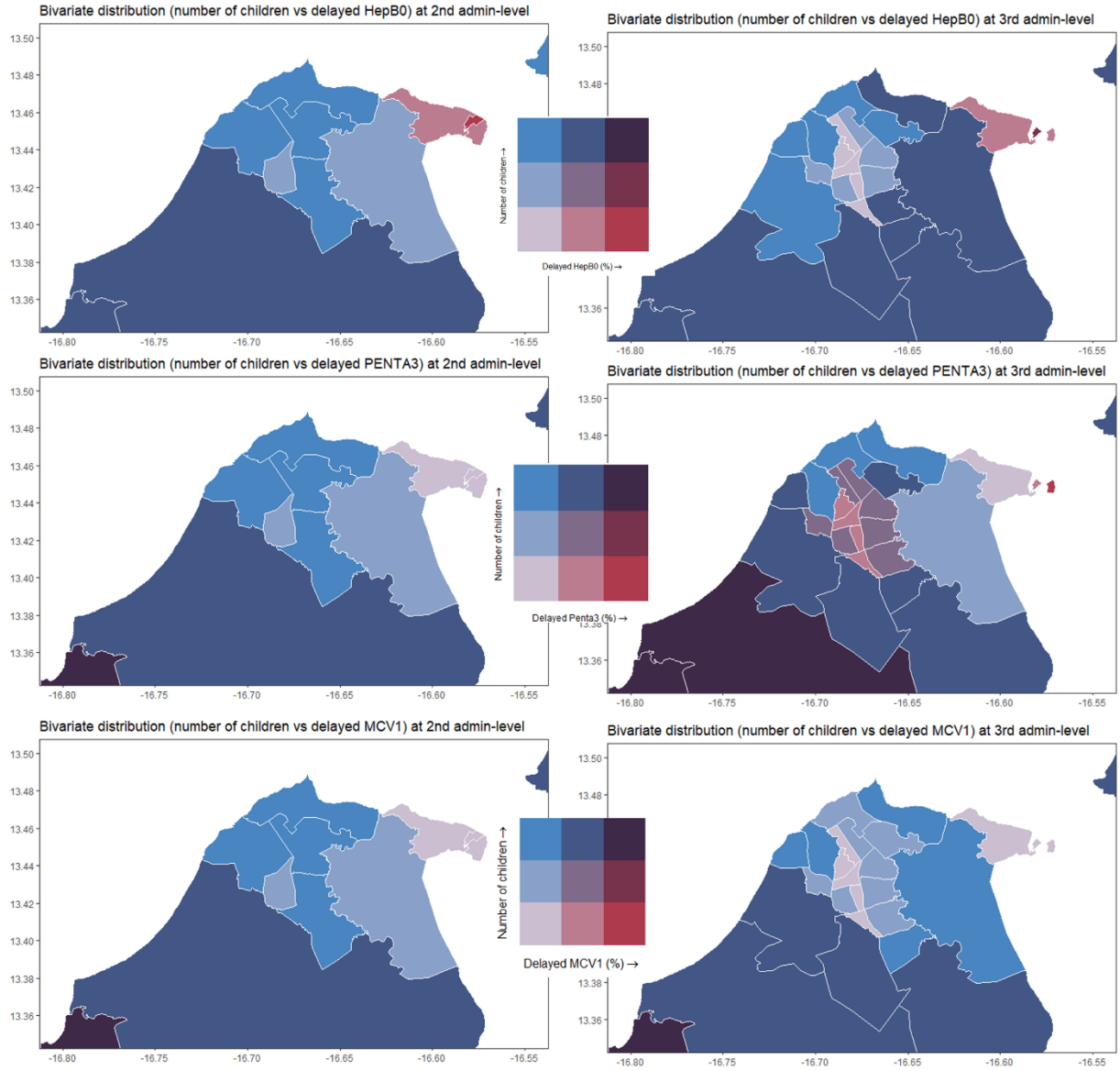


Figure S9: Zoomed in map of districts and wards in the Greater Banjul Area (Banjul and Kanifing LGA) showing; spatial relationships between the prevalence of delayed HepB0 (top row), PENTA3 (middle row), MCV1 (bottom row) and the estimated absolute number of infants with delayed vaccination.

Additional output for the modelled outcome (timely PENTA3 and MCV1)

We decided to model $p(\text{timely vaccination})$ and $p(\text{delayed vaccination})$ because there were more observed cases of both events for both vaccine doses relative to early vaccination. Hence, both timeliness indicators were more likely to be better explained by the covariates included in the analysis. The maps of timely HepB0, PENTA3 and MCV1 are shown below.

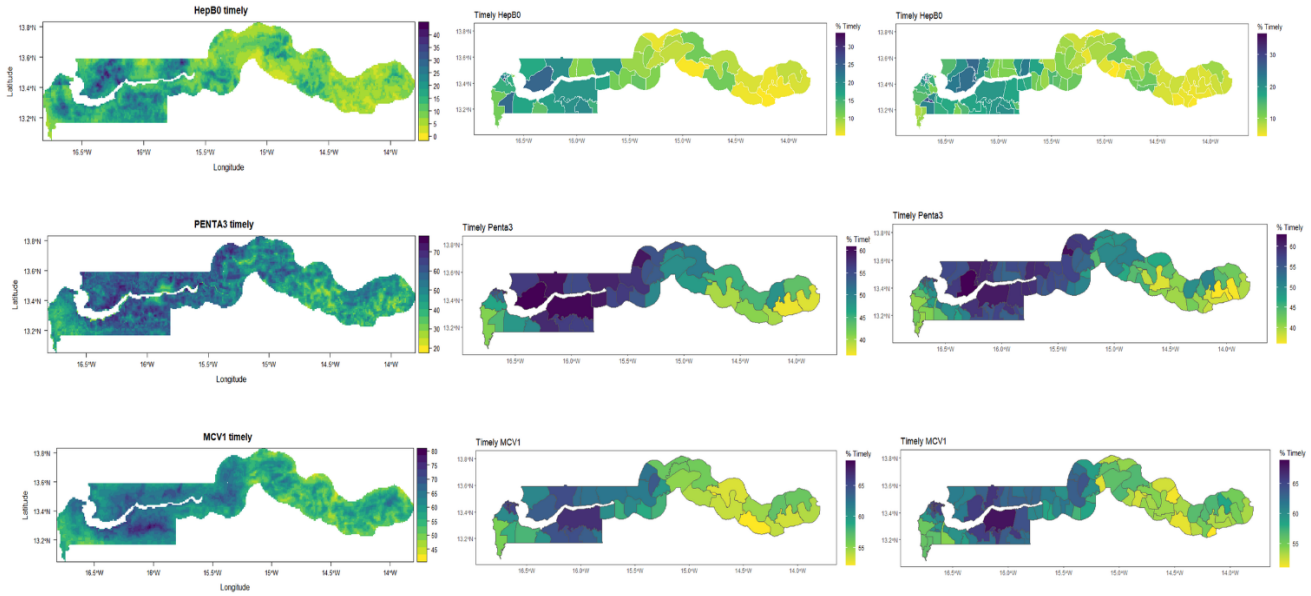


Figure S10: Modelled prevalence of timely HepB0 (top row), PENTA3 (middle row), and MCV1 (bottom row) at 1 x 1 km pixel (left column), district (middle column), ward (right column) level among 12-35 months children in The Gambia, 2019-20

Additional references

1. WorldPop. Geospatial covariate data layers. 2023. https://hub.worldpop.org/project/categories?id=14 (accessed 16 January 2023).
2. Matérn B. Spatial variation: Springer Science & Business Media; 2013.
3. Lindgren F, Rue H, Lindström J. An explicit link between Gaussian fields and Gaussian Markov random fields: the stochastic partial differential equation approach. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2011; **73**(4): 423-98.
4. Simpson D, Rue H, Riebler A, Martins TG, Sørbye SH. Penalising model component complexity: A principled, practical approach to constructing priors. 2017.
5. Fuglstad G-A, Simpson D, Lindgren F, Rue H. Constructing priors that penalize the complexity of Gaussian random fields. *Journal of the American Statistical Association* 2019; **114**(525): 445-52.
6. Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. *Journal of the royal statistical society: Series b (statistical methodology)* 2009; **71**(2): 319-92.
7. Utazi CE, Wagai J, Pannell O, et al. Geospatial variation in measles vaccine coverage through routine and campaign strategies in Nigeria: Analysis of recent household surveys. *Vaccine* 2020; **38**(14): 3062-71.
8. Utazi CE, Aheto JMK, Wigley A, et al. Mapping the distribution of zero-dose children to assess the performance of vaccine delivery strategies and their relationships with measles incidence in Nigeria. *Vaccine* 2023; **41**(1): 170-81.
9. Lumley T. Analysis of Complex Survey Samples. *Journal of Statistical Software* 2004; **9**(8): 1 - 19.
10. Lindgren F, Rue H. Bayesian spatial modelling with R-INLA. *Journal of statistical software* 2015; **63**: 1-25.

Appendix 9: Chapter 5 (Research Paper Supplementary material)

Impact of the COVID-19 pandemic on the coverage and timeliness of routine childhood vaccinations in The Gambia, 2015 – 2021

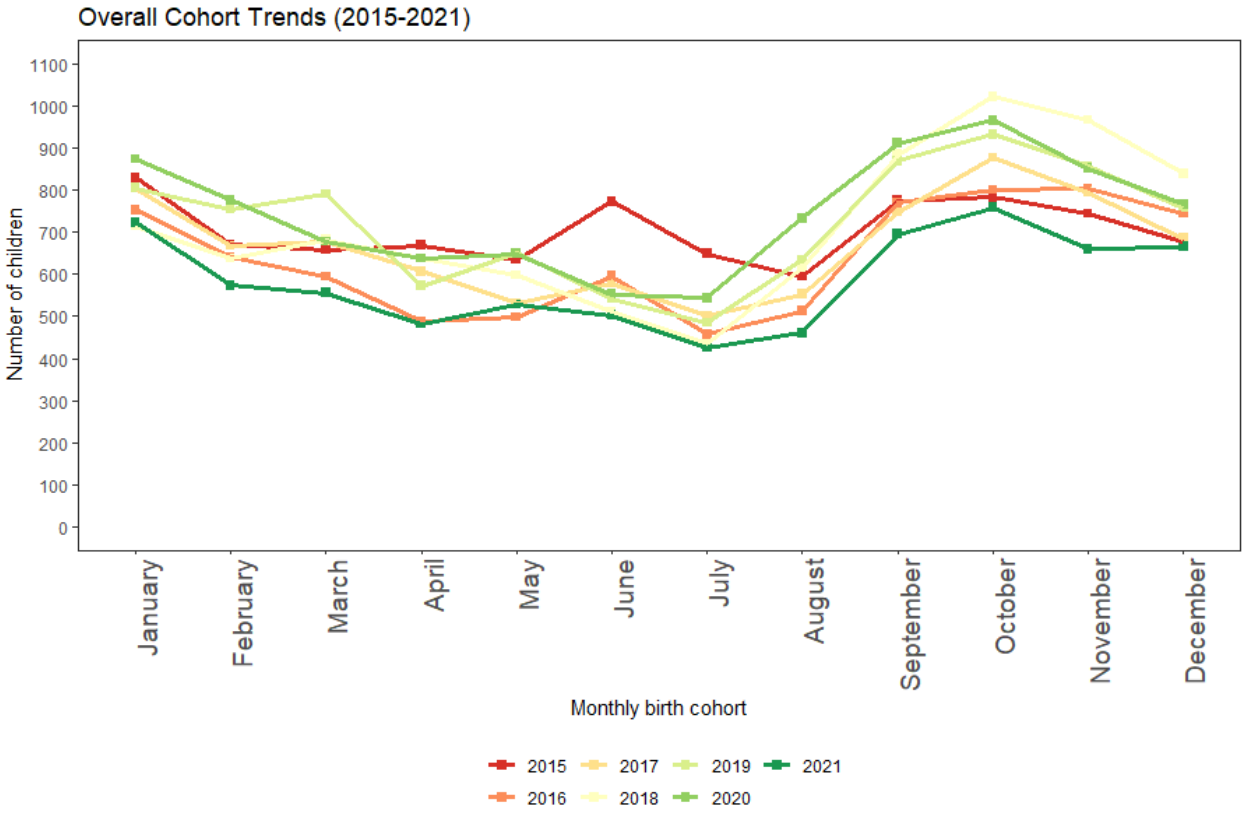
Oghenebrume Wariri, Chigozie Edson Utazi, Uduak Okomo, Alieu Sowe, Malick Sogur, Sidat Fofana, Esu Ezeani, Lamin Saidy, Golam Sarwar, Bai-Lamin Dondeh, Kris A Murray, Chris Grundy, Beate Kampmann

Monthly birth cohort of children included per month, 2015 – 2021 (overall)

Table S1: Detailed information about the number of eligible children per month from the two Health and Demographic Health System in The Gambia (overall), 2015 – 2021

	Years included in the analysis and eligible children						
Months	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
January	829	753	803	714	805	873	723
February	670	641	667	637	755	776	573
March	659	594	679	682	790	678	556
April	669	488	607	637	572	637	482
May	635	498	531	598	650	649	528
June	773	596	579	511	541	552	503
July	649	457	502	435	485	544	425
August	596	513	552	615	634	733	461
September	775	769	747	884	869	911	695
October	782	800	877	1021	932	965	758
November	744	803	795	966	856	851	660
December	676	744	685	839	757	766	665
Total	**8457**	**7656**	**8024**	**8539**	**8646**	**8935**	**7029**

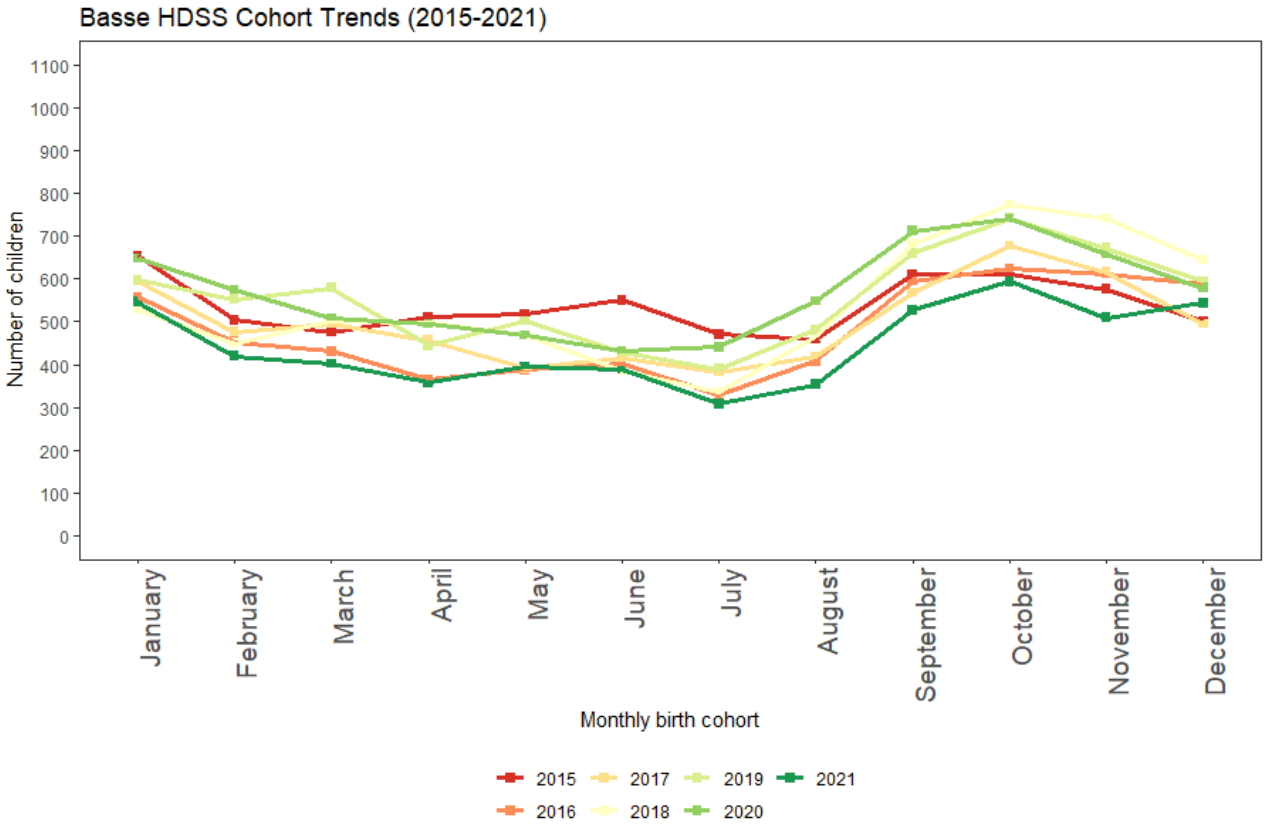
Overall, 57,286 children were included in this analysis spanning 2015 – 2021 (i.e., 5 years before and 2 years into the pandemic)



Monthly birth cohort of children included per month, 2015 – 2021 (Basse)

Table S2: Detailed information about the number of eligible children per month from the Basse Health and Demographic Health System in The Gambia, 2015 – 2021

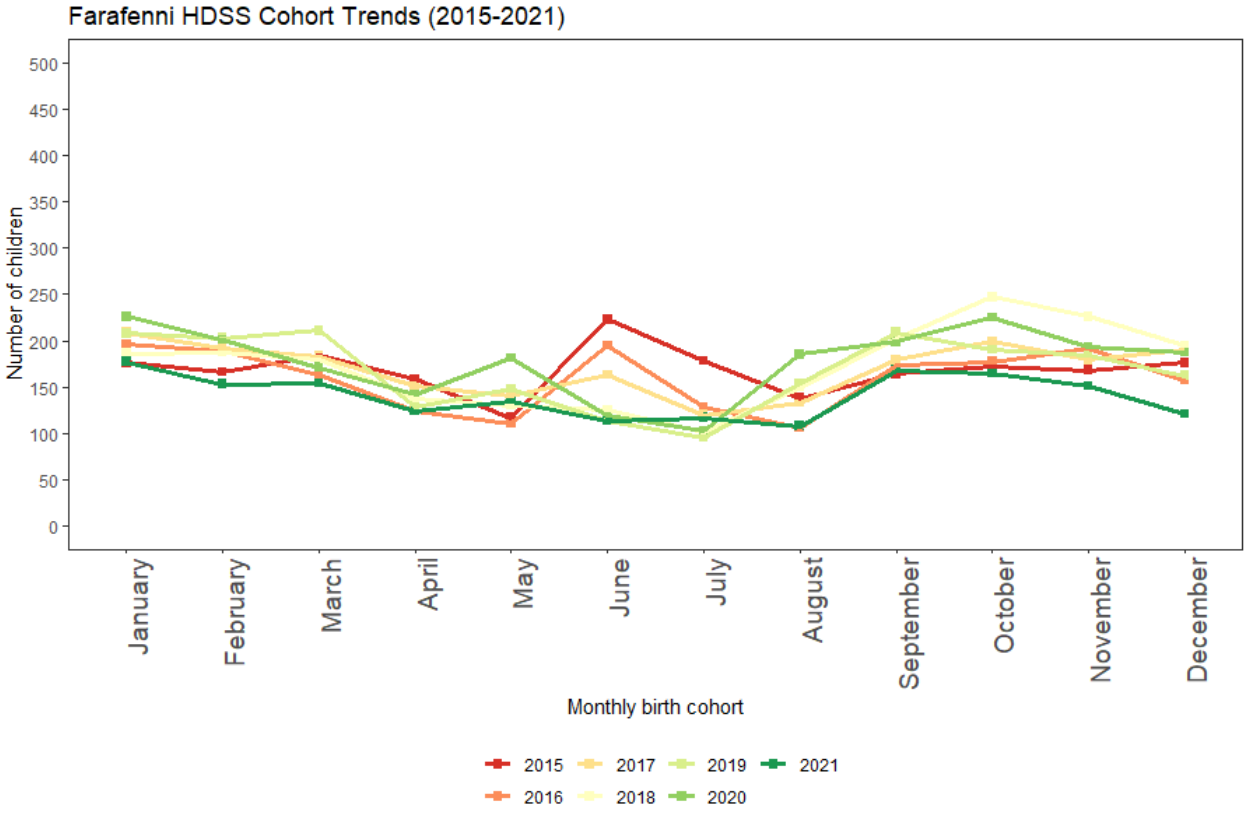
	Years included in the analysis and eligible children						
Months	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
January	653	557	594	528	597	647	546
February	504	453	476	450	552	575	420
March	475	431	496	502	579	507	402
April	511	364	456	499	444	495	358
May	518	388	391	468	502	468	394
June	550	401	416	386	427	432	389
July	471	329	382	334	390	441	308
August	458	407	419	465	480	548	353
September	611	595	568	682	660	712	527
October	610	623	678	774	742	740	593
November	576	612	616	740	672	658	509
December	500	587	495	644	595	579	544
Total	**6437**	**5747**	**5987**	**6472**	**6640**	**6802**	**5343**



Monthly birth cohort of children included per month, 2015 – 2021 (Farafenni)

Table S3: Detailed information about the number of eligible children per month from the Farafenni Health and Demographic Health System in The Gambia, 2015 – 2021

	Years included in the analysis and eligible children						
Months	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
January	176	196	209	186	208	226	177
February	166	188	191	187	203	201	153
March	184	163	183	180	211	171	154
April	158	124	151	138	128	142	124
May	117	110	140	130	148	181	134
June	223	195	163	125	114	120	114
July	178	128	120	101	95	103	117
August	138	106	133	150	154	185	108
September	164	174	179	202	209	199	168
October	172	177	199	247	190	225	165
November	168	191	179	226	184	193	151
December	176	157	190	195	162	187	121
Total	**2020**	**1909**	**2037**	**2067**	**2006**	**2133**	**1686**



Reasons and numbers of children excluded from the analysis

Table S3: Reasons and numbers of children excluded from the timeliness analysis in Farafenni, Basse, and Overall, January 2015 – December 2021

Reasons for exclusion	**Farafenni (N=13,858)** n (%)	**Basse (N=43,428)** n (%)	**Overall (N=57,286)** n (%)
Children with negative vaccination age (HepB0)*	8 (0.06)	321 (0.74)	329 (0.57)
Children with age of hepB0 vaccination more than 150 days**	44 (0.32)	206 (0.47)	250 (0.44)
Children with negative vaccination age (Penta1)*	7 (0.05)	139 (0.32)	146 (0.25)

* These negative age at vaccination (i.e., the difference between the dates of birth and vaccination in days) were likely due to an incorrect date of birth or an incorrect date of vaccination. Because we could not determine which of the two dates was the incorrect one, and because the proportion of affected children was negligible (generally <1%), we decided to exclude them from the timeliness analysis. However, these children were included in the coverage analysis since were certain that they were vaccinated due to the fact that they had a date of vaccination entry.
** We considered that children whose age at HepB) vaccination were >150 days were likely implausible because at that age, they should have received Penta1, Penta2 and Penta3 at 2, 3 and 4 months respectively (60, 90 and 120 days). Although the number of children in this category was negligible (generally <0.5% of the cohort), we considered that such long delays were not likely due to the impact of the pandemic.

Parameter estimates for change in vaccination in Basse HDSS

Table S6: Parameter estimates for the likelihood of change in coverage and the proportion of delayed and early HepB0 and Penta1 vaccinations in the pre-pandemic and pandemic periods in the **Basse HDSS area**

	HepB0			PENTA1		
COVERAGE	**Estimate/Odds ratio**	**95% credible interval**		**Estimate/Odds ratio**	**95% credible interval**	
Level change before 1st wave	1.32	0.84	2.05	1.18	0.75	1.84
Level change before 2nd wave	1.09	0.69	1.69	0.89	0.43	1.75
Level change before 3rd wave	1.49	0.86	2.53	1.19	0.47	2.76
Level change AFTER 3rd wave	**2.21**	**1.24**	**3.89**	0.95	0.34	2.37
Pre-pandemic change in slope	0.99	0.99	1.00	0.98	0.97	1.00
Change in slope before 1st wave	1.06	0.93	1.20	1.00	0.86	1.16
Change in slope before 2nd wave	1.06	0.97	1.15	1.05	0.94	1.18
Change in slope before 3rd wave	1.06	0.92	1.22	1.02	0.87	1.19
Change in slope AFTER 3rd wave	0.93	0.78	1.10	1.11	0.92	1.33
$\hat{\sigma}^{-2}$	37.19	20.50	60.76	13.85	5.24	25.93
ρ̂	0.50	0.21	0.75	0.83	0.67	0.94
DELAYED						
Level change before 1st wave	1.33	0.72	2.46	1.95	0.88	4.55
Level change before 2nd wave	1.41	0.74	2.67	1.12	0.23	4.20
Level change before 3rd wave	1.23	0.58	2.63	0.71	0.09	3.34
Level change AFTER 3rd wave	0.61	0.28	1.36	0.85	0.08	4.56
Pre-pandemic change in slope	**0.97**	**0.97**	**0.98**	1.00	0.98	1.04
Change in slope before 1st wave	1.02	0.85	1.22	0.82	0.61	1.08
Change in slope before 2nd wave	0.97	0.86	1.09	0.92	0.75	1.13
Change in slope before 3rd wave	0.85	0.71	1.01	0.99	0.75	1.31
Change in slope AFTER 3rd wave	1.09	0.87	1.35	0.90	0.64	1.25
$\hat{\sigma}^{-2}$	21.50	9.98	41.54	4.47	1.38	9.17
ρ̂	0.54	0.09	0.85	0.82	0.60	0.96
EARLY						
Level change before 1st wave				**0.20**	**0.05**	**0.76**
Level change before 2nd wave				0.42	0.15	1.18
Level change before 3rd wave				**0.09**	**0.02**	**0.47**
Level change AFTER 3rd wave				0.45	0.10	1.98
Pre-pandemic change in slope				0.99	0.99	1.00
Change in slope before 1st wave				1.21	0.85	1.73
Change in slope before 2nd wave				0.94	0.75	1.18
Change in slope before 3rd wave				1.43	0.93	2.26
Change in slope AFTER 3rd wave				0.90	0.53	1.51
$\hat{\sigma}^{-2}$				7.73	4.56	12.14
ρ̂				0.26	-0.07	0.58

Parameter estimates for change in vaccination in Farafenni HDSS

Table S5: Parameter estimates for the likelihood of change in coverage and the proportion of delayed and early HepB0 and Penta1 vaccinations in the pre-pandemic and pandemic periods in the **Farafenni HDSS area**

	HepB0			PENTA1		
COVERAGE	**Estimate/Odds ratio**	**95% credible interval**		**Estimate/Odds ratio**	**95% credible interval**	
Level change before 1st wave	1.01	0.45	2.30	1.14	0.42	3.12
Level change before 2nd wave	2.33	0.88	6.11	3.91	0.92	16.00
Level change before 3rd wave	**2.54**	**1.14**	**11.12**	3.03	0.54	16.04
Level change AFTER 3rd wave	2.29	0.69	7.70	2.97	0.46	17.51
Pre-pandemic change in slope	0.98	0.97	1.00	0.97	0.95	1.13
Change in slope before 1st wave	1.16	0.91	1.49	1.21	0.87	1.68
Change in slope before 2nd wave	1.04	0.87	1.24	1.00	0.78	1.28
Change in slope before 3rd wave	0.87	0.66	1.13	0.97	0.69	1.37
Change in slope AFTER 3rd wave	1.06	0.75	1.48	0.91	0.60	1.39
$\hat{\sigma}^{-2}$	8.25	4.29	13.54	3.54	1.65	6.01
$\hat{\rho}$	0.63	0.40	0.82	0.74	0.56	0.88
DELAYED						
Level change before 1st wave	0.97	0.36	2.74	0.87	0.45	1.61
Level change before 2nd wave	2.60	0.84	8.22	1.12	0.72	1.75
Level change before 3rd wave	2.37	0.60	9.57	1.79	0.91	3.50
Level change AFTER 3rd wave	0.38	0.09	1.54	1.38	0.63	3.03
Pre-pandemic change in slope	0.98	0.96	1.00	1.00	0.99	1.00
Change in slope before 1st wave	1.14	0.85	1.55	1.12	0.95	1.35
Change in slope before 2nd wave	0.87	0.71	1.05	1.02	0.93	1.13
Change in slope before 3rd wave	**0.72**	**0.54**	**0.95**	0.88	0.71	1.08
Change in slope AFTER 3rd wave	1.07	0.78	1.46	0.88	0.65	1.19
$\hat{\sigma}^{-2}$	7.99	2.93	18.52	31.75	12.16	74.18
$\hat{\rho}$	0.79	0.43	0.96	-0.14	-0.59	0.36
EARLY						
Level change before 1st wave				1.58	0.45	5.59
Level change before 2nd wave				**0.23**	**0.06**	**0.85**
Level change before 3rd wave				1.87	0.43	8.23
Level change AFTER 3rd wave				0.50	0.08	3.01
Pre-pandemic change in slope				1.00	0.99	1.01
Change in slope before 1st wave				0.86	0.59	1.23
Change in slope before 2nd wave				1.31	0.99	1.68
Change in slope before 3rd wave				0.74	0.47	1.12
Change in slope AFTER 3rd wave				1.01	0.53	1.90
$\hat{\sigma}^{-2}$				6.83	3.11	13.19
$\hat{\rho}$				0.50	0.14	0.78

Extra Results: Changes in Penta1 timely vaccination due to the pandemic and counterfactual scenario overall (i.e., Basse and Farafenni HDSS combined)

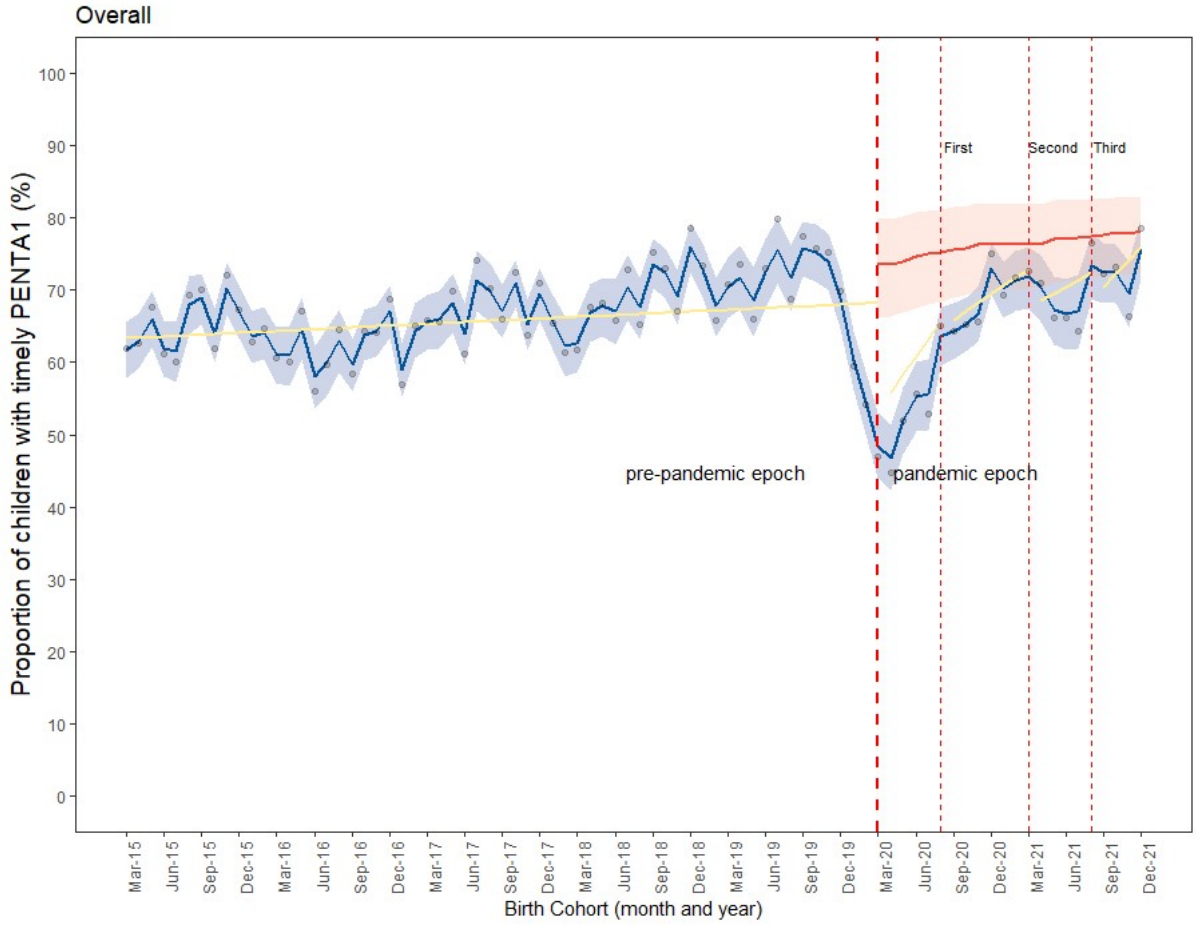


Table S7: Parameter estimates for the likelihood of change in timely Penta1 (OverLL)

OVERALL	Odds ratio/Estimate	95% Credible Interval (lower and upper)	
Level change before 1st wave	0.53	0.27	1.03
Level change before 2nd wave	0.83	0.41	2.01
Level change before 3rd wave	0.93	0.41	2.42
Level change AFTER 3rd wave	0.95	0.39	2.61
Pre-pandemic change in slope	1.00	0.99	1.01
Change in slope before 1st wave	1.10	0.92	1.33
Change in slope before 2nd wave	1.05	0.92	1.20
Change in slope before 3rd wave	1.04	0.86	1.27
Change in slope AFTER 3rd wave	1.09	0.86	1.40

*Non of the parameter estimates are significant because the credible intervals include 1.00.

Extra Results: Changes in Penta1 timely vaccination due to the pandemic and counterfactual scenario in Basse HDSS area

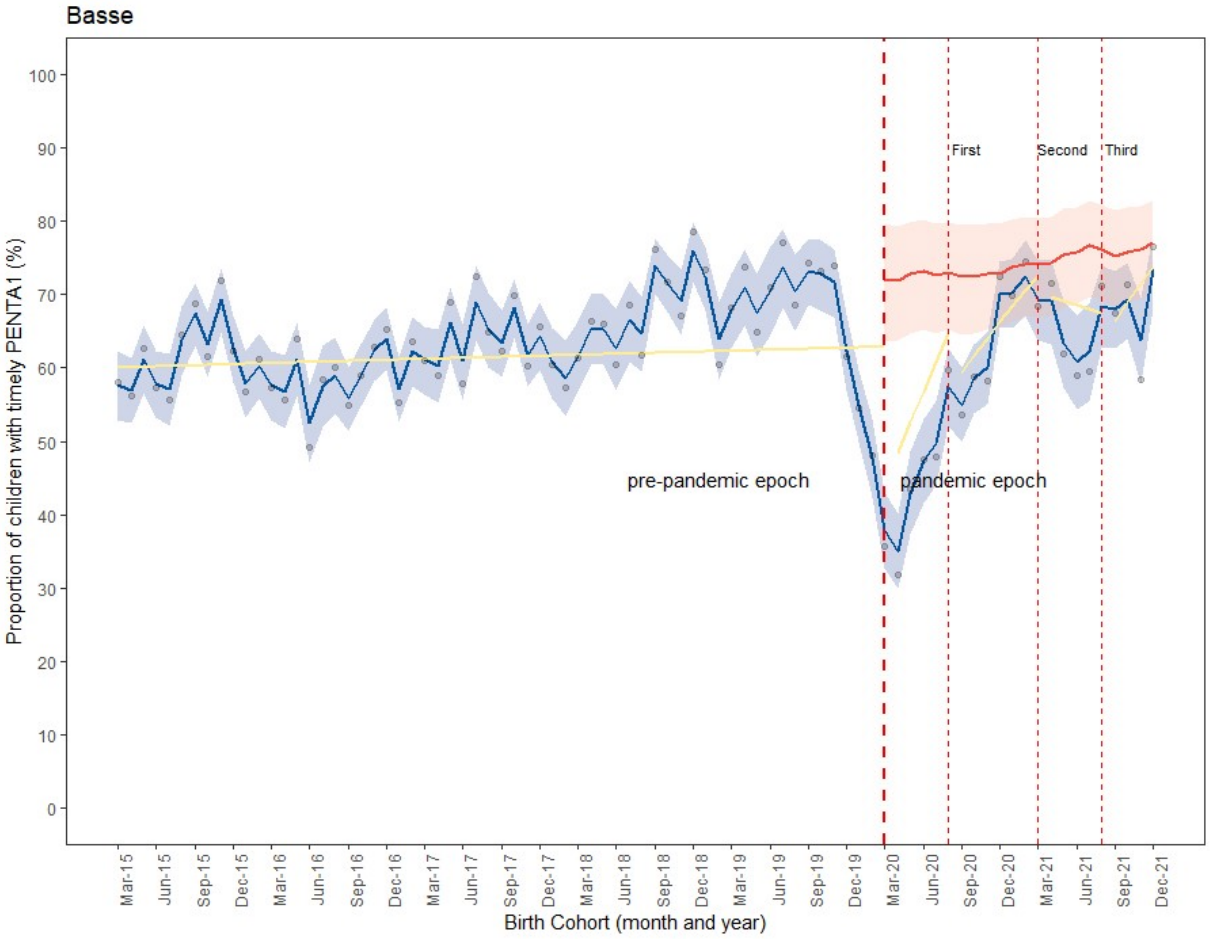


Table S8: : Parameter estimates for the likelihood of change in timely Penta1 (Basse)

Parameters	Odds ratio/Estimate	95% Credible Interval (lower and upper)	
Level change before 1st wave	0.47	0.21	1.00
Level change before 2nd wave	0.77	0.29	2.66
Level change before 3rd wave	1.36	0.44	5.93
Level change AFTER 3rd wave	1.00	0.30	4.96
Pre-pandemic change in slope	1.00	0.98	1.02
Change in slope before 1st wave	1.18	0.94	1.49
Change in slope before 2nd wave	1.10	0.93	1.30
Change in slope before 3rd wave	0.97	0.77	1.23
Change in slope AFTER 3rd wave	1.12	0.84	1.50

*None of the parameter estimates are significant because the credible intervals include 1.00.

Extra Results: Changes in Penta1 timely vaccination due to the pandemic and counterfactual scenario in Farafenni HDSS area

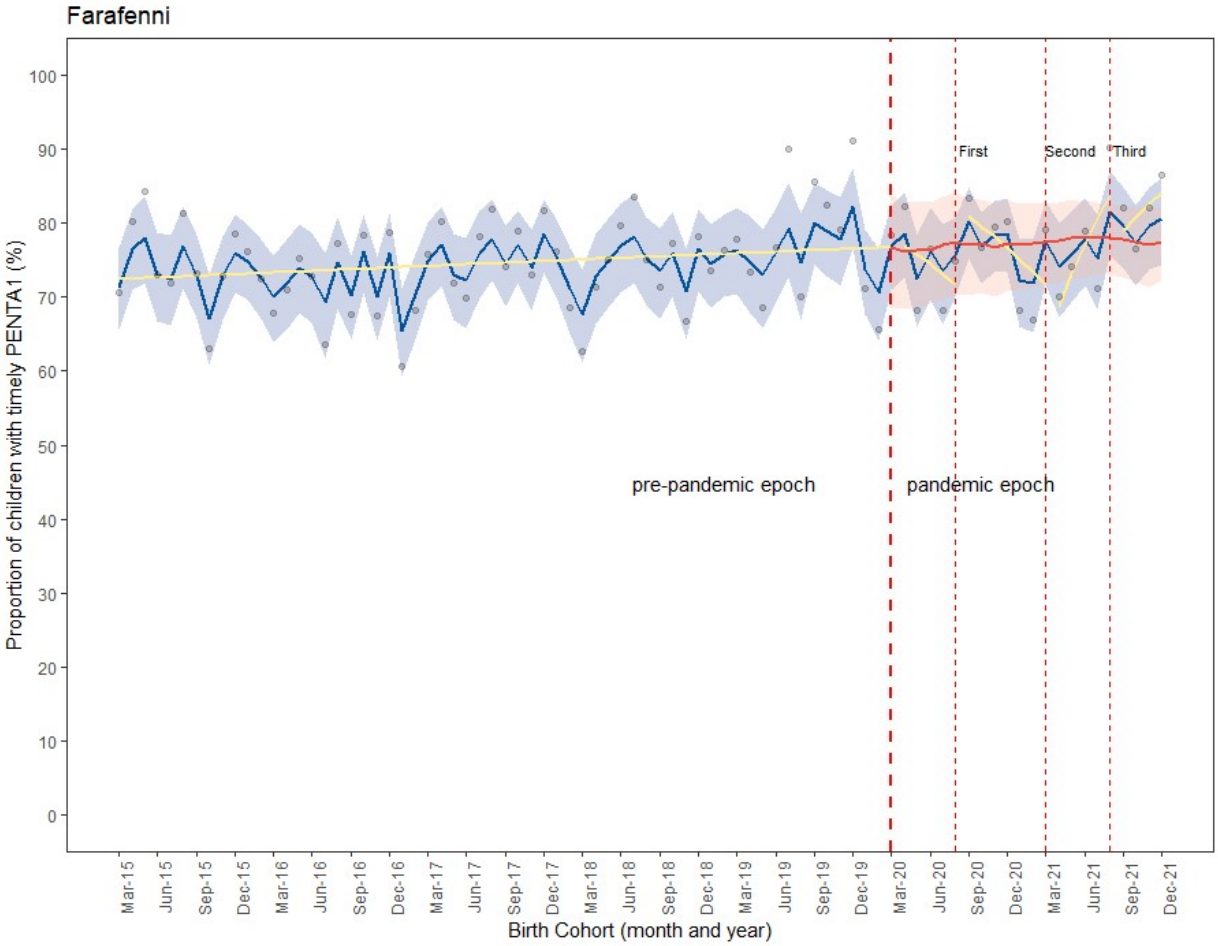


Table S9: Parameter estimates for the likelihood of change in timely Penta1 (Farafenni)

Parameters	Odds ratio/Estimate	95% Credible Interval (lower and upper)	
Level change before 1st wave	1.08	0.53	2.25
Level change before 2nd wave	1.37	0.77	2.42
Level change before 3rd wave	0.51	0.24	1.10
Level change AFTER 3rd wave	0.94	0.38	2.31
Pre-pandemic change in slope	1.01	0.99	1.02
Change in slope before 1st wave	0.93	0.75	1.14
Change in slope before 2nd wave	0.91	0.81	1.03
Change in slope before 3rd wave	1.23	0.98	1.56
Change in slope AFTER 3rd wave	1.12	0.81	1.57

*Non of the parameter estimates are significant because the credible intervals include 1.00.

Appendix 10: Chapter 6 (Research Paper Supplementary material)

Multi-level determinants of timely routine childhood vaccinations in The Gambia: findings from a nationwide analysis

Oghenebrume Wariri MD, Chigozie Edson Utazi PhD, Uduak Okomo PhD, Winfred Dotse-Gborgbortsi PhD, Malick Sogur MSc, Sidat Fofana MSc, Prof Kris A Murray PhD, Chris Grundy MSc, Prof Beate Kampmann PhD

Methodology of the 2019-20 The Gambia Demographic and Health Survey

The 2019-20 Gambia Demographic and Health Survey (GDHS) employed a two-stage stratified sampling design to generate national, Local Government Area (LGA), and urban/rural-representative estimates of health and demographic indicators, including vaccination data.[1] This design involved dividing each of the eight LGAs (Banjul, Basse, Brikama, Janjanbureh, Kanifing, Kerewan, Kuntaur, and Mansakonko) into urban and rural areas and then drawing samples from each stratum in two stages. In the first stage, survey clusters were selected with probability proportional to size within each sampling stratum using a national sampling frame. The second stage involved randomly selecting households from household lists within the chosen clusters. The 2019-20 GDHS also collected the GPS location of all survey clusters.

To ensure respondent confidentiality, DHS randomly displaced the GPS coordinates (longitude and latitude) of survey clusters.[2] This displacement was up to 2 kilometres for urban clusters and up to 5 kilometres for rural clusters, with a small subset (1%) of rural clusters displaced up to 10 kilometres. Importantly, the displacement ensured that points remained within the country, within the DHS survey region (or LGA), and within the second administrative area (district).[2] Therefore, the displaced cluster's coordinates corresponded to the same administrative levels as the undisplaced cluster.

The 2019-20 GDHS covered 281 clusters and 7,025 households and data was collected between November 21, 2019, and March 30, 2020.[1] Childhood immunisation data for children aged 0-35 months who received vaccines at any time before the survey was collected based on mothers' recall or from parent-held vaccination cards. However, determining vaccination timeliness required date of birth and vaccination dates from home-based vaccination records (HBR).[3] Thus, our analysis focused on the 3,248 children (93% of 12-35-month-olds) with complete birth and vaccination dates from their HBR. We also obtained the GPS locations (latitude and longitude) of each cluster where these children resided after obtaining explicit approval from the DHS programme.

Detailed description of covariates and outcome variables

Table S1: Description and coding of covariate factors and outcome variables

Variable or covariate	Relevant DHS variable(s) code	Description and comments
Sex of child	B4	Sex of child (Male and Female).
Place of birth	M15	Provides information about where the child was born. All children born at “Home” and “Other home”, “Other” were classified as being born at **Home**. Those born in any form of facility (public sector, private sector, NGO, etc.) were classified as being born in a **Health facility**.
Season of birth	B1	This variable was determined based on the child's month of birth, considering the Gambia's seasonal pattern. In the Gambia, the wet season runs from June to October, while the dry season spans from November to May.[4] Therefore, children were categorized based on their birth month, aligning with these distinct seasons
Birth order	BORD	Birth order of the child, in numbers ranging from 1:20. This was reclassified into three categories: 1-2, 3-5, and >5.
Ethnicity	V131	To simplify the analysis of ethnic groups in The Gambia, categories were combined based on their prevalence in the data. Ethnic groups with individual representations less than 2% – namely, Bambara, Creole/Aku Marabout, Jola/Karoninka, Manjago, and Serere – were collectively classified as 'Others.
Religion	V130	Categories created based on the major religions practised in The Gambia, i.e., Islam and Christianity.
Region	V024	This variable indicates the Administrative Level One (Admin 1) regions in The Gambia. For analytical purposes, we made two adjustments: first, Banjul and Kanifing were combined to form 'Greater Banjul', and second, the three easternmost regions – Kuntaur, Janjanbureh, and Basse – were grouped together as 'Other Regions'. This grouping was motivated by two reasons: 1) our previous analysis identified these three regions as having the lowest timely vaccination rates compared to other regions,[5] and 2) the initial analysis where we did not combine the regions had wide confidence intervals for the outcomes, although the results were similar with the final analysis. Thus, merging the regions allowed for more precise results (i.e., narrower confidence intervals) while maintaining consistency with our earlier findings.
Urban/Rural	V025	Categories included Rural – 0, Urban – 1
Maternal age	V012	Maternal age was reclassified into 15-19 (≤19), 20-29, 30-39, and 40-49.
Timeliness of previous Penta dose		This variable indicates whether the previous dose of the multi-series pentavalent vaccine, Penta 1, Penta 2 and Penta 3, was received within the recommended time frame. 'Untimely' refers to previous Penta (i.e., Penta1/Penta2) administered either before the minimum acceptable age (early) or after the maximum acceptable age (delayed), as defined by the national immunisation schedule.
Parity	V201	Indicates maternal parity, in numbers ranging from 1:20. This was reclassified into two categories: 1-3, and ≥4.

ANC number*	M14	This variable indicates the number of maternal antenatal care (ANC) visits attended during pregnancy. It was recategorized into two groups: 1-3 ANC visits and 4 or more ANC visits.
PNC attendance*	M70	This variable indicates whether the baby received a postnatal check (PNC) within two months of birth. The response options were 'Yes' or 'No.
Maternal education	V106	The maternal education categories were reclassified into three levels: no education, primary education, and secondary/higher education. This was done by merging the secondary and higher education categories into one group
Marital status		This variable categorized maternal marital status into three distinct groups: 'Never in union', 'Married/with partner' (combining married and Living with partner), and 'Divorced/widowed/separated' (combining those who are widowed, divorced, or no longer living together/separated)
Maternal bank account	V170	Has an account in a bank or other financial institutions. The variable was coded as 0 = No and 1 = Yes.
Maternal health insurance	V481	Indicates if a household covered by health insurance. The variable was coded as 0 = No and 1 = Yes.
Sex of household head	V151	Indicates the sex of the head of the household
Household size	V136	The variable represents the number of household members, ranging from 1 upwards. It was reclassified into three categories for analysis: 'Small' (1-4 members), 'Medium' (4-8 members), and 'Large' (more than 8 members).
Wealth index	V190A	The wealth index, which was standardized by the DHS to allow comparisons between urban and rural areas. We recategorized this variable into three distinct groups for this analysis: 'Poor' (combining the poorest and poorer categories); 'Middle'; and 'Rich' (combining the richest and richer categories).
Household media exposure	V157, V158, V159	This composite variable was constructed based on the frequency of household media exposure, encompassing newspaper reading (V157), radio listening (V158), and television viewing (V159). Individuals that responded "Not at all" to all three media exposure variables were classified as having “No media exposure”. Otherwise, they were classified as “Media exposed”.
Household own mobile phone	V169A	Indicates if household owns a mobile telephone. The variable was coded as 0 = No and 1 = Yes.
Household own bed nets	V459	Indicates if a household have mosquito bed net for sleeping. The variable was coded as 0 = No and 1 = Yes.
Length of stay	V104	This variable indicates the number of years a household has resided in their current dwelling. It was categorized into four groups: less than 1 year (combining visitors and those who have stayed less than 1 year), 1 to 3 years, 4 to 5 years, and more than 5 years (combining those who have always lived in their residence and those who have stayed for more than 5 years).
Distance to clinic as an issue?	V467D	This variable represents the perceived difficulty in accessing medical care at a healthcare facility (i.e., perceived distance to facility). It was coded as "Big problem" and "Not a big problem".

Household own motorized vehicle	V124 & V125	This variable indicates whether a household owns a motorized vehicle, such as a motorcycle/scooter (V124) or a car/truck (V125). Households that responded "Yes" to either of these two variables were classified as owning a motorized vehicle (Yes), while those that answered "No" to both variables were classified as not owning a motorized vehicle (No).
Travel time - multimodal	NA	This variable represents the estimated travel time to the nearest fixed immunisation clinic from the DHS cluster an individual was from. The travel time was calculated assuming a multi-modal mode of transportation, incorporating both walking and motorized options. The modelled travel time (in minutes) was categorized into three groups: less than 30 minutes, 30 to less than 60 minutes, and more than 60 minutes.
Nearest clinic type	NA	This variable represents the type of the nearest clinic to the DHS cluster from which an individual was surveyed. Two options were available: "Outreach Site" or "Health Facility (i.e. fixed clinic)"
Nearest clinic open weekly	NA	This variable indicates whether at minimum, the nearest clinic to the DHS cluster operates on a weekly basis for immunisation services as per their service schedule. Two options were available: 'Yes' or 'No'."
Nearest clinic has cold store	NA	This variable indicates whether the nearest clinic to the DHS cluster has an on-site cold storage facility for vaccine storage. Two options were available: 'Yes' or 'No'.
Nearest clinic vaccination staff	NA	This variable represents the number of vaccine delivery staff at the nearest clinic to the DHS cluster. These numbers were reclassified into two categories: 'One staff member' or 'Two or more staff members'.
Catchment population around nearest clinic	NA	This variable serves as a proxy indicator for potential waiting times at clinics within the catchment area of the nearest clinic to the DHS cluster. We hypothesized that clinics with a larger population in their catchment area may have longer waiting times due to higher demand. To assess this, the number of people in the catchment area was divided into three terciles, resulting in three categories: 'Low', 'Medium', and 'High'.
Service availability & readiness	NA	This composite variable was constructed based on five factors: the type of the nearest clinic, its weekly operation for immunisation services, the presence of an on-site cold storage facility, the number of vaccine delivery staff, and the population size within the catchment area. The lowest score is zero (0) and the highest possible score was 5, indicating that the nearest clinic is a fixed health facility, operates at minimum weekly, has a cold store, has two or more staff members, and serves a low-to-medium catchment population. Subsequently, three categories were created: 'Low' (0-1), 'Intermediate' (2-3), and 'High' (4-5).
Timely HepB0	H50D, H50M, H50Y, B17, B1, and B2	This outcome variable, representing the age (in days) at the time of HepB0 vaccine receipt, was calculated by subtracting the day, month, and year of birth (B17, B1, and B2) from the day, month, and year of HepB0 receipt (H50D, H50M, and H50Y). The age at HepB0 receipt was then compared to the national immunisation window of 24 hours of birth (i.e., 1 day). Vaccines administered within the 24-hour window were classified as 'Timely', while those received outside this window were considered 'Untimely'.

Timely Penta 1	H51D, H51M, H51Y, B17, B1, and B2	This outcome variable, representing the age (in days) at the time of Penta 1 vaccine receipt, was calculated by subtracting the day, month, and year of birth (B17, B1, and B2) from the day, month, and year of HepB0 receipt (H51D, H51M, and H51Y). The age at Penta 1 receipt was then compared to the national immunisation window of 61 – 90 days (i.e., at 2 months). Vaccines administered within this window were classified as 'Timely', while those received outside this window (early or delayed) were considered 'Untimely'.
Timely Penta 2	H52D, H52M, H52Y, B17, B1, and B2	This outcome variable, representing the age (in days) at the time of Penta 2 vaccine receipt, was calculated by subtracting the day, month, and year of birth (B17, B1, and B2) from the day, month, and year of HepB0 receipt (H52D, H52M, and H52Y). The age at Penta 2 receipt was then compared to the national immunisation window of 91 – 120 days (i.e., at 3 months). Vaccines administered within this window were classified as 'Timely', while those received outside this window (early or delayed) were considered 'Untimely'.
Timely Penta 3	H53D, H53M, H53M, B17, B1, and B2	This outcome variable, representing the age (in days) at the time of Penta 3 vaccine receipt, was calculated by subtracting the day, month, and year of birth (B17, B1, and B2) from the day, month, and year of HepB0 receipt (H53D, H53M, and H53Y). The age at Penta 3 receipt was then compared to the national immunisation window of 121 – 150 days (i.e., at 4 months). Vaccines administered within this window were classified as 'Timely', while those received outside this window (early or delayed) were considered 'Untimely'.
Timely 1st, 2nd & 3rd dose of Penta	NA	This composite variable assesses whether a child received all three doses of the Penta vaccine in a timely manner It was constructed based on the individual timely status for each dose (Timely Penta1, Timely Penta2, and Timely Penta3). Two categories were defined: "Timely," indicating that all three doses were administered on time, and "Untimely," indicating that at least one dose was administered outside the recommended timeframe. This outcome variable evaluates a child's ability to consistently receive the multi-dose Penta vaccine according to the recommended schedule.
Timely MCV1	H9D, H9M, H9Y, B17, B1, and B2	This outcome variable, representing the age (in days) at the time of MCV1 vaccine receipt, was calculated by subtracting the day, month, and year of birth (B17, B1, and B2) from the day, month, and year of HepB0 receipt (H9D, H9M, and H9Y). The age at MCV1 receipt was then compared to the national immunisation window of 271 – 300 days (i.e., at 9 months). Vaccines administered within this window were classified as 'Timely', while those received outside this window (early or delayed) were considered 'Untimely'.

* Despite being well-established predictors of childhood vaccination uptake, the covariates 'ANC number' (antenatal care) and 'PNC attendance' (postnatal care) were excluded from the final analysis due to their high missingness rates of 17% each. This decision was made to prevent potential reductions in statistical power, biased estimates, and inaccurate standard errors from the multi-level regression model.

The Gambia national immunisation facility mapping and census

To enhance microplanning for vaccination services, The Gambia's EPI programme, in collaboration with Crosscut (https://crosscut.io/), undertook an immunisation facility mapping and census aimed at generating a comprehensive national geolocated database of immunisation facilities. The process of generating the national geolocated database of immunisation facilities in The Gambia began in early 2019 and concluded later that year.

The process of creating the final National Geolocated Immunisation Facility Dataset involved four primary steps:

1. Identification and Compilation: Crosscut, responsible for executing the facility census and mapping, closely collaborated with national programme managers of The Gambian EPI to compile a comprehensive list of all facilities (government or private) providing routine childhood vaccination services, including health facilities and immunisation outreach posts.
2. Verification: The initial facility list underwent thorough verification by cross-referencing unique facility names with immunisation focal persons across all the regional health directorates in The Gambia. This process ensured that the list compiled at the national level, reflected the current realities at the regional level because some facilities might have been closed while new ones might have also been opened.
3. Primary Data Collection: Crosscut and EPI focal persons conducted on-site visits to all the facility on the verified list for primary data collection. This process included obtaining geolocation coordinates (i.e., longitude and latitude), photographing each unique facility, and gathering facility attribute information such as type, ownership, and the availability of functional vaccine cold storage.
4. Additional Analysis: Further analysis was conducted on the primary data to derive additional information, such as estimating the population of children within the catchment area of each immunisation facility. Population estimates from WorldPop were utilized, employing a travel-time least-cost-path model to delineate catchment areas and assign population grids to their respective immunisation sites.

To further augment the dataset with crucial information needed for this study, In 2021, we collaborated with The Gambian EPI to update the national geolocated dataset of immunisation facilities with additional variables which we considered very important supply-side determinants of vaccination. This included variables such as the number of days per month a facility was operational and staffing levels for vaccination service provision for all the facilities on the database. During this process, we ensured continued engagement with EPI focal persons both nationally and across all regional health directorates in The Gambia. Through this process, we verified all the information, starting with the immunisation programme managers at the national level, and then, the immunisation focal persons at the regional health directorates.

Spatial location of all immunisation clinics in The Gambia

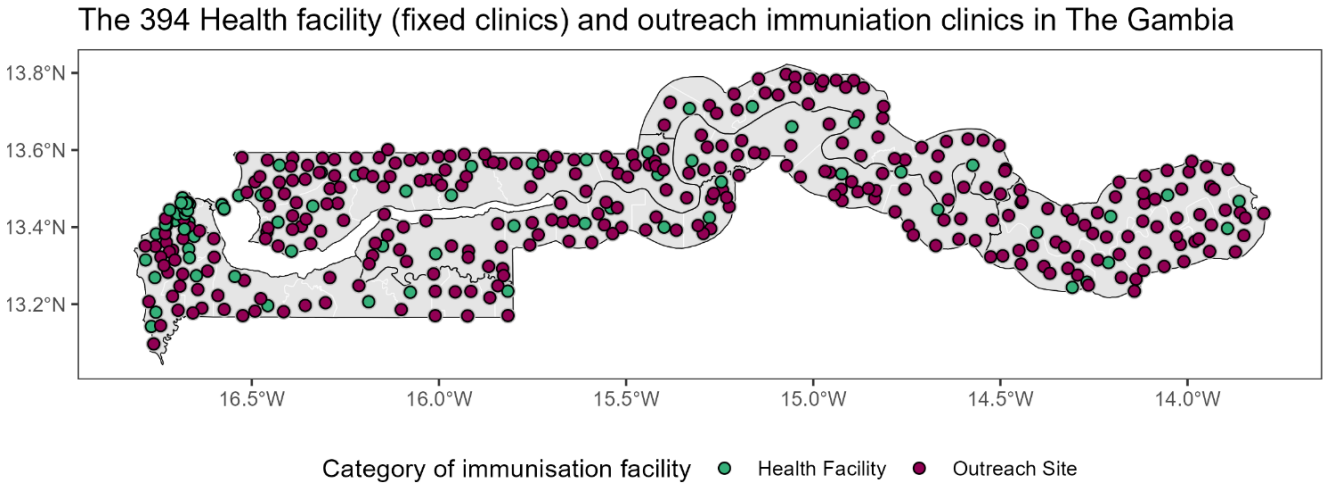


Fig S1: The spatial locations of all 394 immunisation facilities (fixed and outreach sites) in The Gambia as of December 2019. The shapefiles for creating these maps we obtained from the global database of Global Administrative areas (GADM) (https://gadm.org/data.html). The maps were created in R.

Modelling geographic accessibility

We used travel time to the nearest immunisation clinics as the indicator of choice to determine geographic accessibility. We chose travel time as it considers various factors, including elevation, barriers, road network, and travel speed, which collectively influence geographic accessibility more accurately than Euclidean or straight-line distances.[6] AccessMod, a GIS tool developed by WHO, was employed to model travel time to immunisation clinics and analyze geographic accessibility.[7] AccessMod was selected due to its widespread usage, simplicity, and availability as free software for modelling geographic accessibility to health services in several sub-Saharan Africa.[8-11] We considered two travel scenarios; (1) to the nearest fixed immunisation clinic or outreach immunisation site (i.e., any facility) and, (2) to the nearest fixed immunisation clinic alone.

The travel time modelling utilized raster and vector data encompassing land cover, digital elevation model (DEM), road networks, water bodies, and the locations of immunisation clinics. Openly available land cover data were obtained from the European Space Agency,[12] while road network data was sourced from OpenStreetMap (OSM),[13] and the DEM for The Gambia was acquired from DIVA-GIS.[14] To ensure compatibility, all datasets were re-projected to a consistent coordinate system and resolution of 1km x 1km. Travel times were computed as the least-cost path over an impedance surface, which involved a gridded map layer representing travel speed.

Initially, we generated an integrated gridded friction surface in AccessMod5.0 by combining the land cover grid with other landscape elements, including barriers like water bodies, along with the road network (trunks, primary, secondary, tertiary roads, etc.). Subsequently, a travel scenario was defined to determine travel speeds on different land cover and road types, incorporating both motorized and walking journeys (i.e., multi-modal approach) to the nearest immunisation clinic. Walking travel speeds were assigned based on maximum speeds of 5 km/h on grassland, built-up areas, and footpaths; 4 km/h on shrubland, cropland, tree cover, bare and sparse vegetation; and 3 km/h on herbaceous and mangroves.[15] Motorized travel speeds on roads were assigned conservatively using calibrated speed limits (S3 Table), based on travel time studies conducted in similar African context.[15,16] For non-motorized/walking travel, Tobler's function was applied to account for speed variations when ascending or descending slopes, depending on the direction of travel.[17] Barriers such as water bodies were considered traversable only when crossed by bridges.

Travel time was generated at 1 km resolution and extracted using the corresponding cluster locations from The Gambia Demographic and Health Survey (DHS) 2019-2020. Median travel times were extracted within 5 km and 2 km buffer zones for rural and urban clusters, respectively, to account for the deliberate displacement of cluster locations applied in the DHS methodology for respondent confidentiality.[18]

Table S2: Travel speed assigned to land cover and road types

Description	Land cover or road class	Speed in (km/hr)	Mode of travel
Landcover	Herbaceous and Mangroves	3	Walking
	Tree cover, Shrubland, Cropland, Bare and sparse vegetation	4	Walking
	Grassland and Built-up area	5	Walking
	Permanent water bodies or rivers	0	Walking
Road	Footpath, footway, path, pedestrian way	5	Walking
	Tracks	5	Walking
	Tertiary roads	25	Motorized
	Secondary roads	30	Motorized
	Primary roads	48	Motorized
	Trunks	48	Motorized

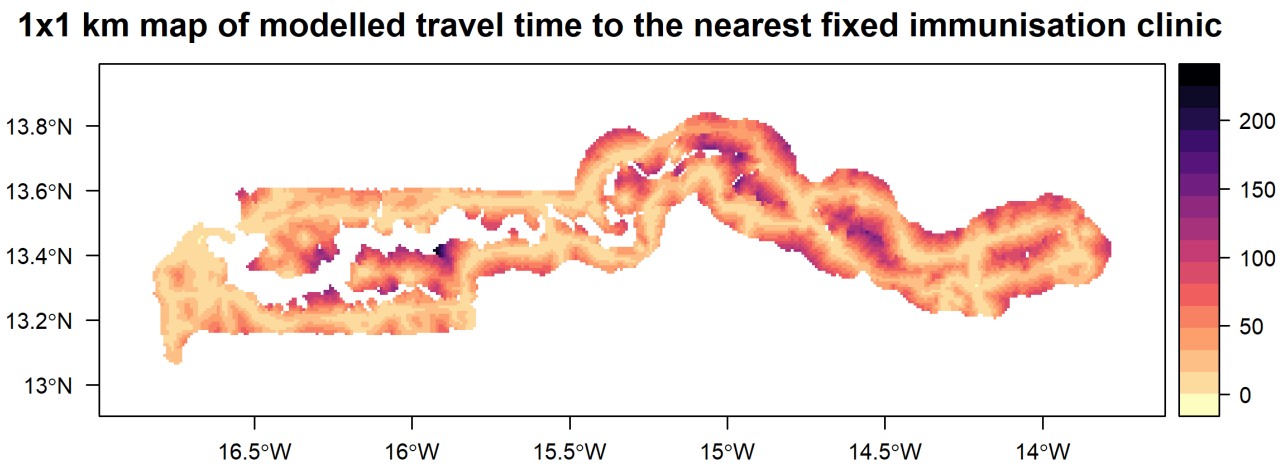


Fig S2: Maps of travel time (in minutes) to the nearest fixed immuniation clinic in The Gambia at 1km x 1km. The shapefiles for creating these maps were obtained from the global database of Global Administrative areas (GADM) (https://gadm.org/data.html). The maps were created in R.

DHS cluster-level travel time to the nearest fixed clinic

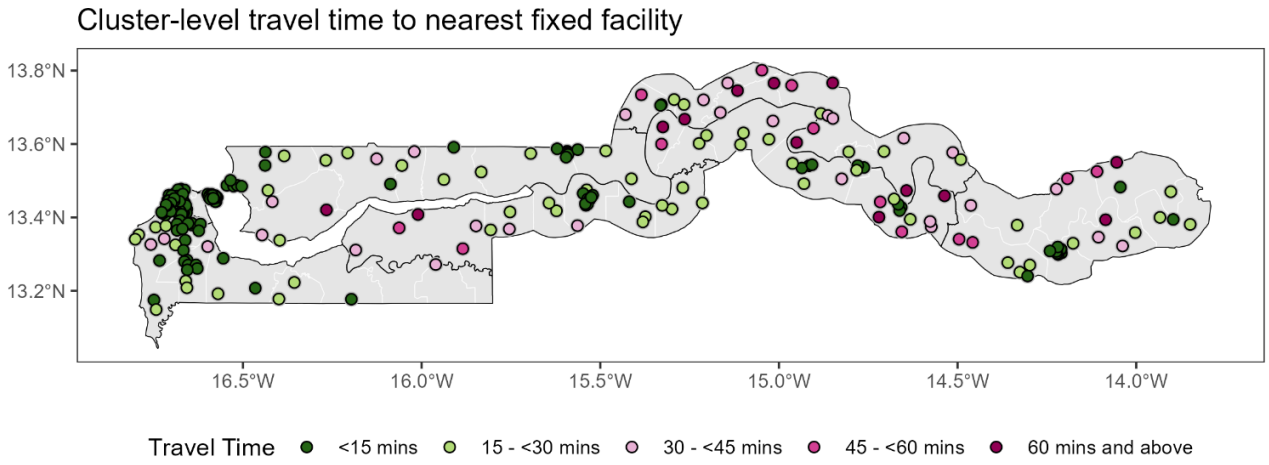


Fig S3: Maps showing travel time (in minutes) from DHS clusters to the nearest fixed immunisation clinic in The Gambia. The shapefiles for creating these maps were obtained from the global database of Global Administrative areas (GADM) (https://gadm.org/data.html). The maps were created in R.

Linking DHS clusters to the nearest immunisation clinic

Using the GPS coordinates of both the clusters geolocation from the 2019-20 The Gambia DHS and national geolocated database of immunisation facilities in The Gambia conducted in 2019, we linked each children from the DHS clusters to the nearest immunisation facility. This allowed us to link every DHS cluster to at least one facility and each child in each DHS cluster to their nearest immunisation clinic, along with detailed information about the facility (i.e., its qualities), including: the facility type, whether it has a functional vaccine cold storage, staffing levels, the population within it's catchment, and it's immunisation service schedule.

To achieve the linkage of DHS clusters to the nearest immunisation facility, we followed these steps:

1. **Impedance surface creation:** We created an impedance surface using elevation, roads, water bodies, and travel speeds, as detailed in the section describing our approach to modelling geographic accessibility (travel time) to immunisation facilities.
2. **Travel time modelling:** Using the impedance surface, we modelled travel time to the DHS cluster locations by accumulating travel costs.
3. **Facility overlay and travel time extraction:** We overlaid the health facility geolocations onto the gridded travel times to each DHS cluster to extract the travel time value and identify the nearest facility to each cluster.
4. **Nearest facility assignment:** Finally, the cluster closest to the facility (in terms of travel time) was assigned as the nearest immunisation clinic for each child within the cluster. We also assigned all the qualities of the nearest immunisation clinic to the children from the clusters which were linked to it.

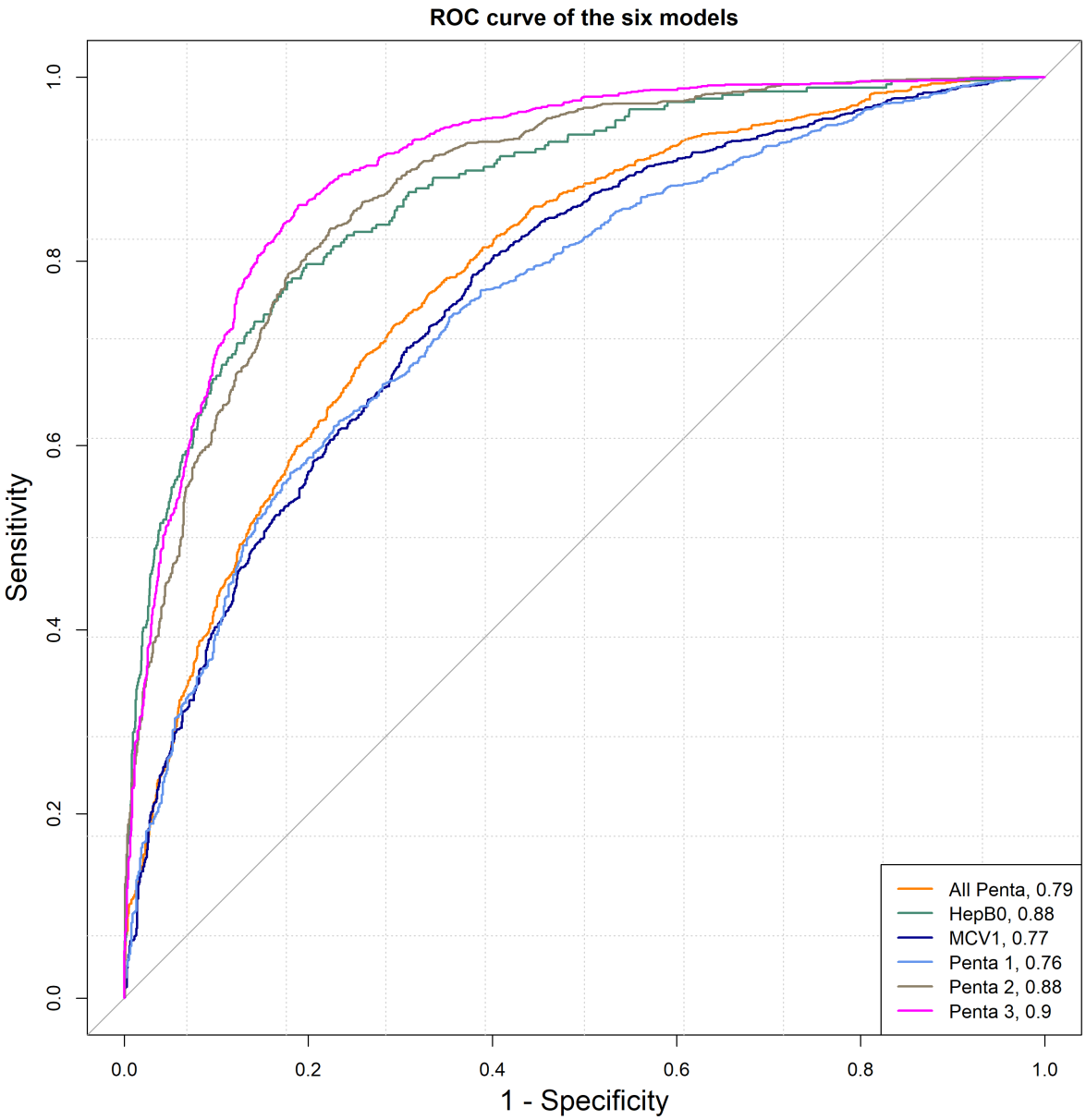


Fig S4: Plots of the area under the receiver operating characteristic curve (ROC) scores of the fitted models. The computed area under the curve (AUC) scores are included in the legends for each vaccine combination.

Variance Coefficient Partition (VPC) for the six multi-level models

For each outcome variable (i.e., timely HepB0, Penta1, Penta2, Penta3, All Penta and MCV1), we assessed the proportion of the total residual variation (after accounting for covariate effects) that can be attributed to different levels of the model's hierarchy using the variance partition coefficient (VPC). [19] The output from the VPC analysis is shown below.

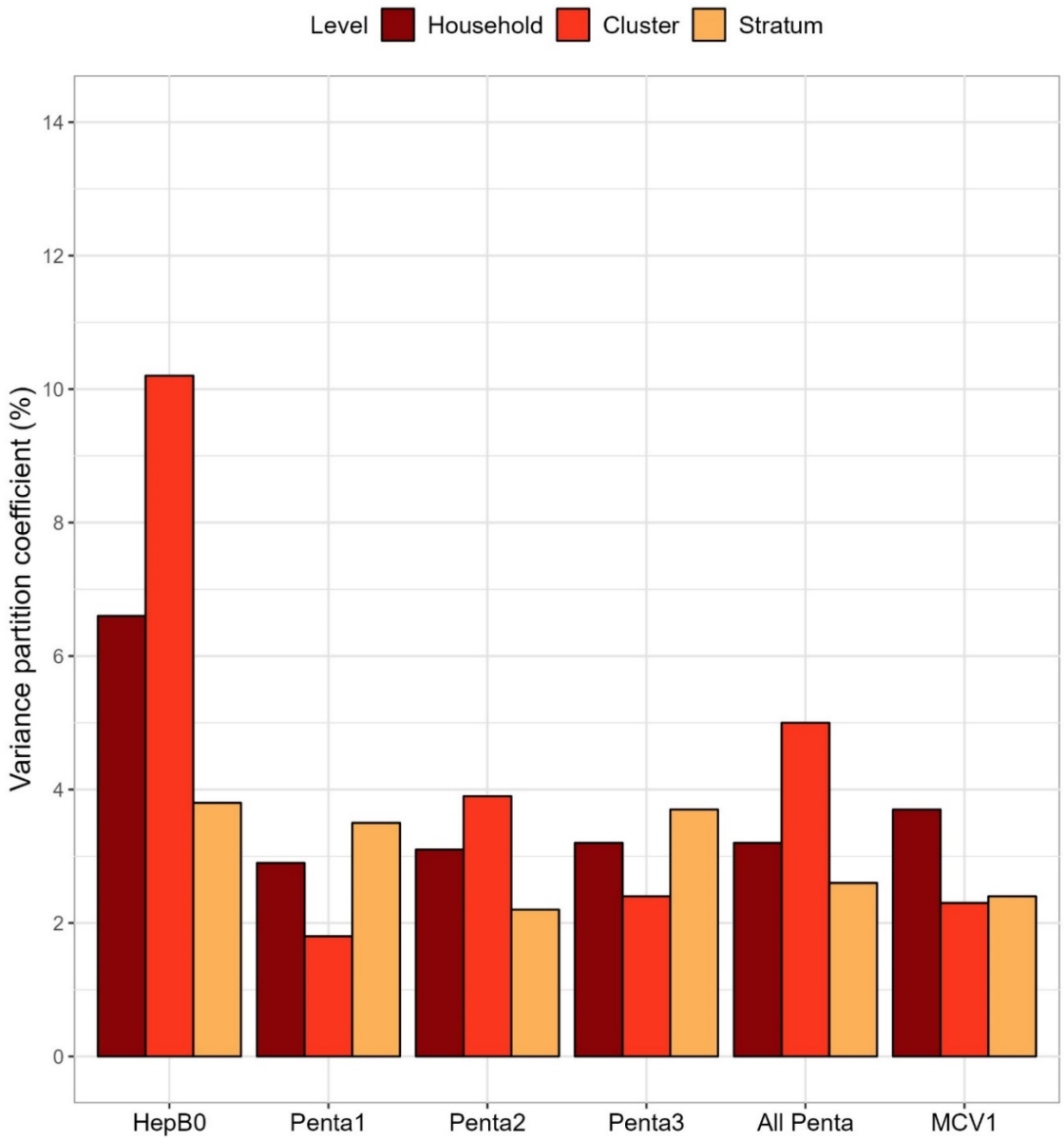


Fig S5: Variance partition coefficient plots showing the proportion of variation in timely vaccination attributable to the different levels of data accounted for in the fitted models.

Fig S5 shows that the cluster-level random effect accounted for most of the unexplained variation in timely HepB0, Penta2, and All Penta vaccinations. However, for timely Penta1 and Penta3, the stratum-level random effect explained most of the residual variations, while the household-level random effect explained MCV1. The presence of higher unexplained variation in the odds of timely vaccination across the different levels suggests the need to identify additional predictors of timely vaccination specific to those levels. This finding also underscores the importance of spatially-detailed estimates of vaccination timeliness, allowing for interventions targeted at finer geographic scales.

Unadjusted bivariate analysis of factors associated with timely HepB0

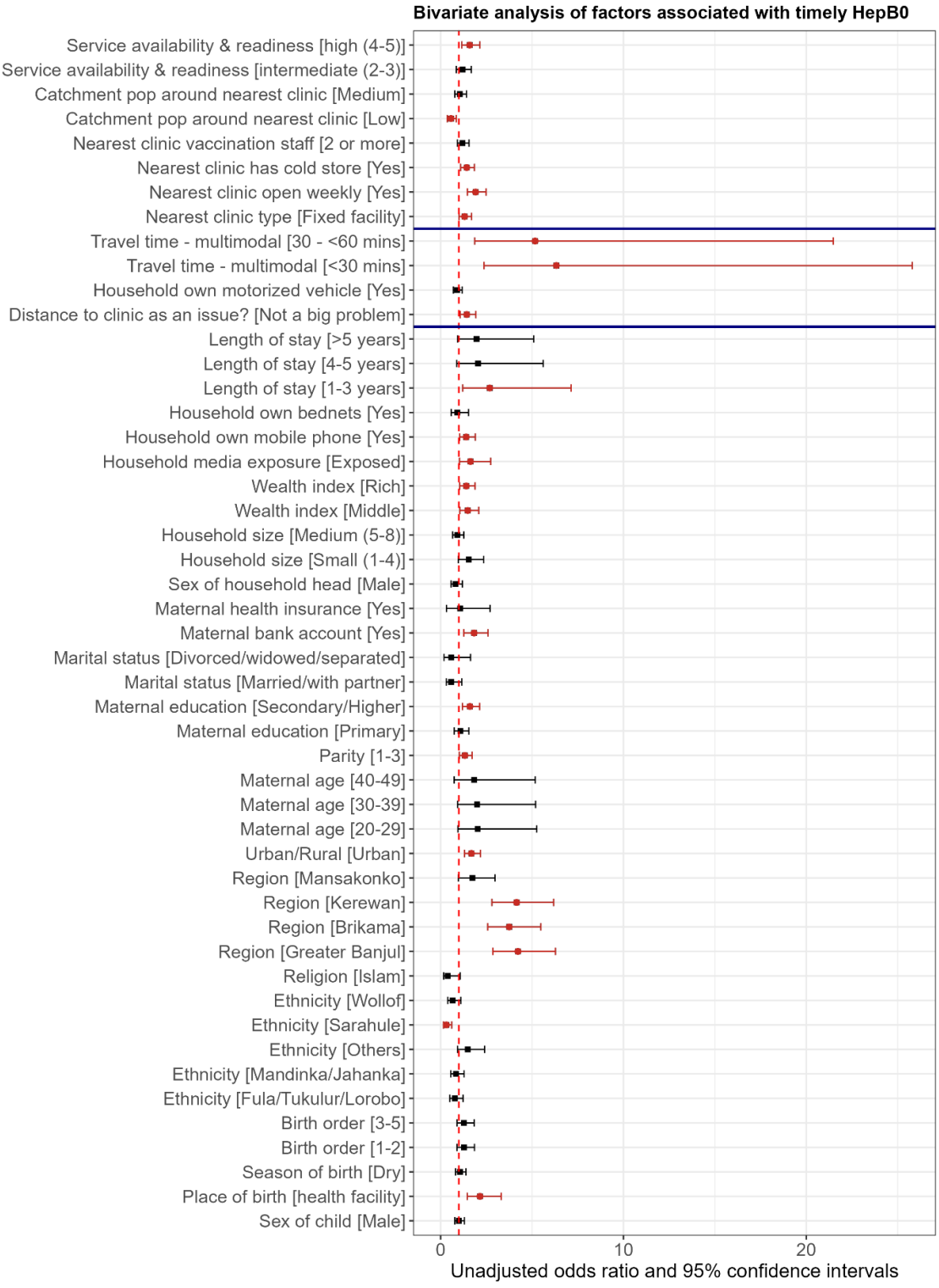


Fig S6: Unadjusted odds ratio and corresponding 95% credible interval plots for determinants of timely birth-dose of hepatitis B (HepB0). Note: The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Unadjusted bivariate analysis of factors associated with timely Penta 1

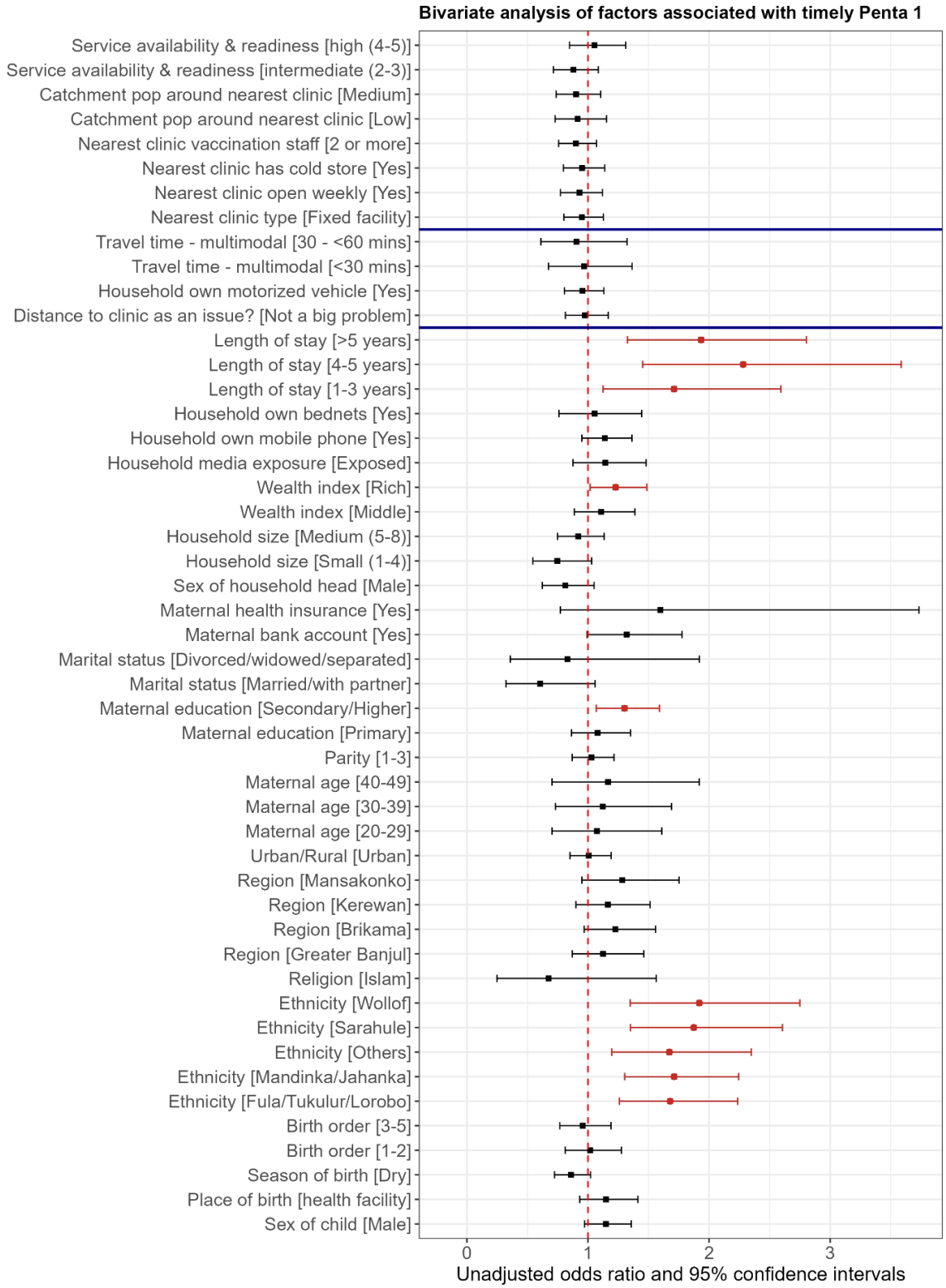


Fig S7: Unadjusted odds ratio and corresponding 95% credible interval plots for determinants of timely first-dose of pentavalent vaccine (Penta1). Note: The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Unadjusted bivariate analysis of factors associated with timely Penta 2

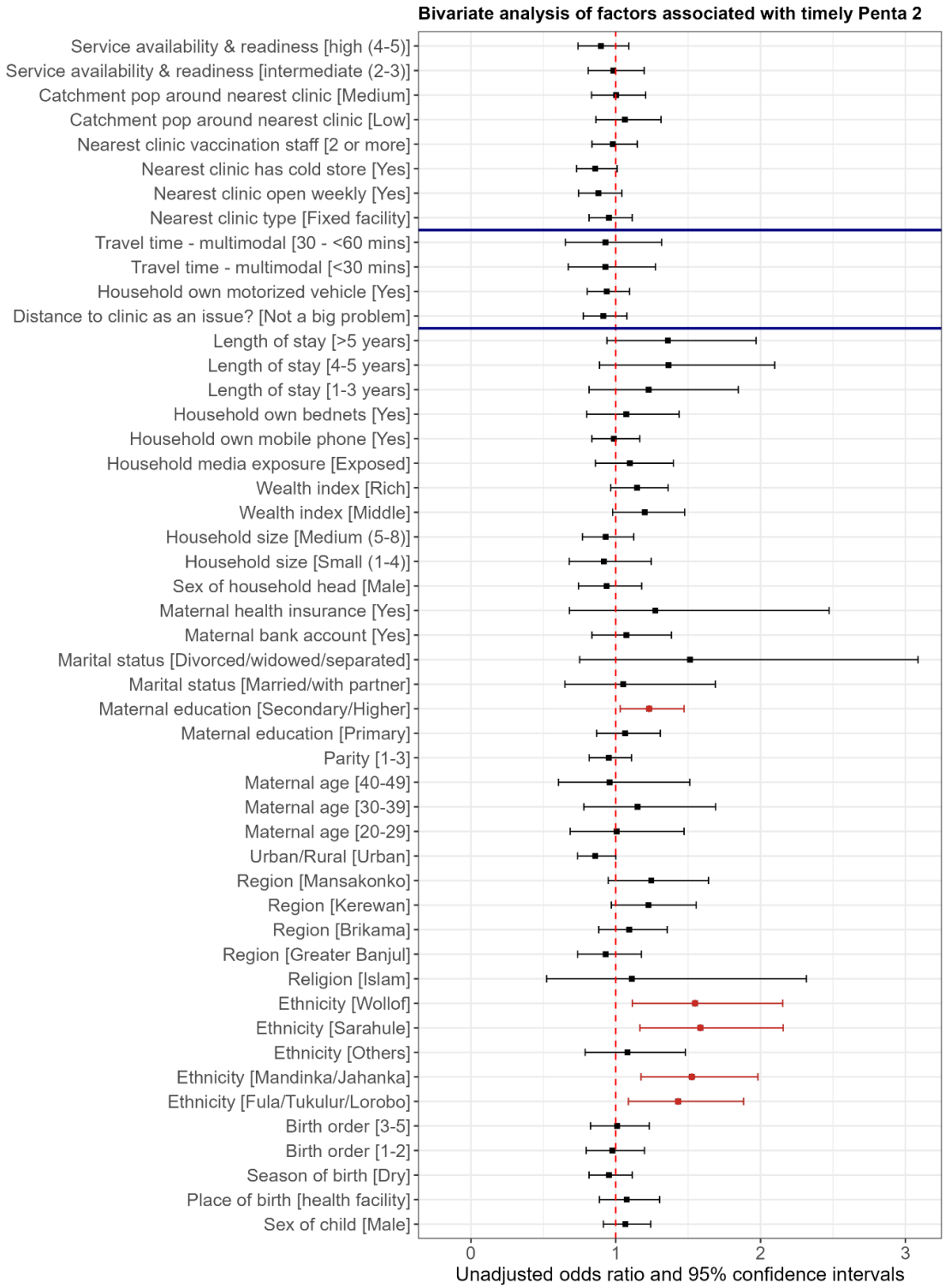


Fig S8: Unadjusted odds ratio and corresponding 95% credible interval plots for determinants of timely second-dose of pentavalent vaccine (Penta2). Note: The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Unadjusted bivariate analysis of factors associated with timely Penta 3

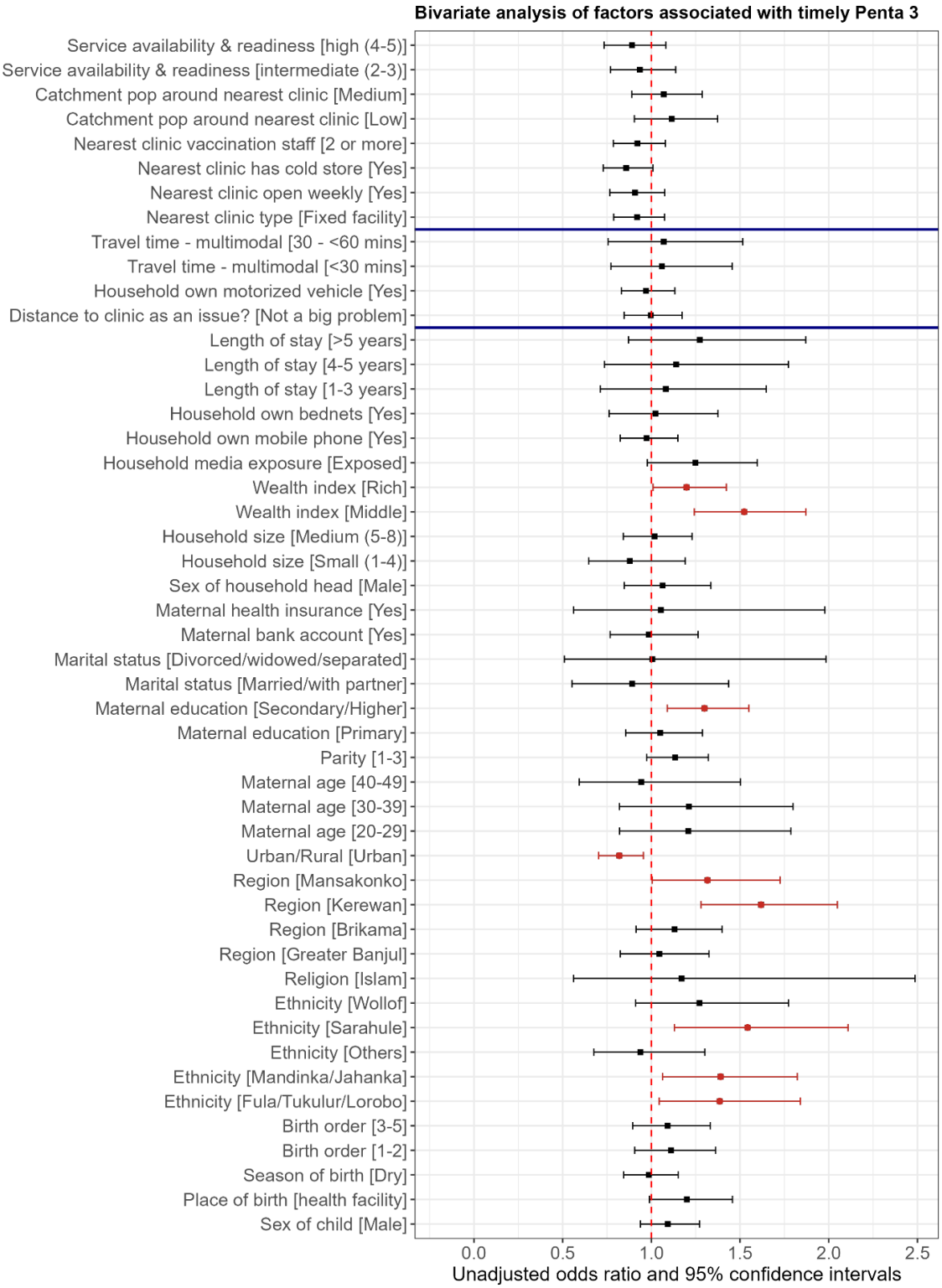


Fig S9: Unadjusted odds ratio and corresponding 95% credible interval plots for determinants of timely third-dose of pentavalent vaccine (Penta3). Note: The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Unadjusted bivariate analysis of factors associated with timely ‘All Penta’

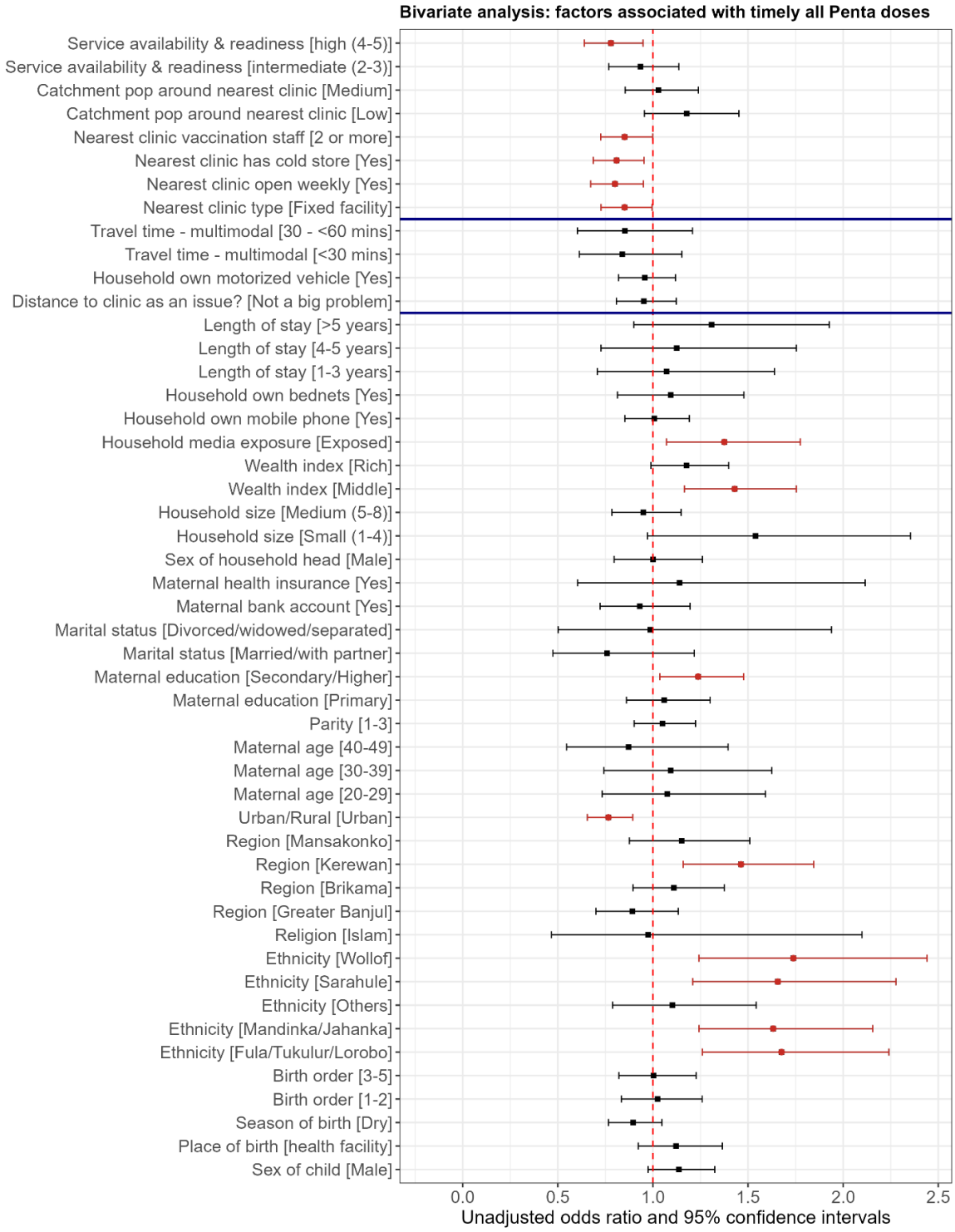


Fig S10: Unadjusted odds ratio and corresponding 95% credible interval plots for determinants of timely all doses of pentavalent vaccine (‘All Penta’). Note: The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

Unadjusted bivariate analysis of factors associated with timely MCV1

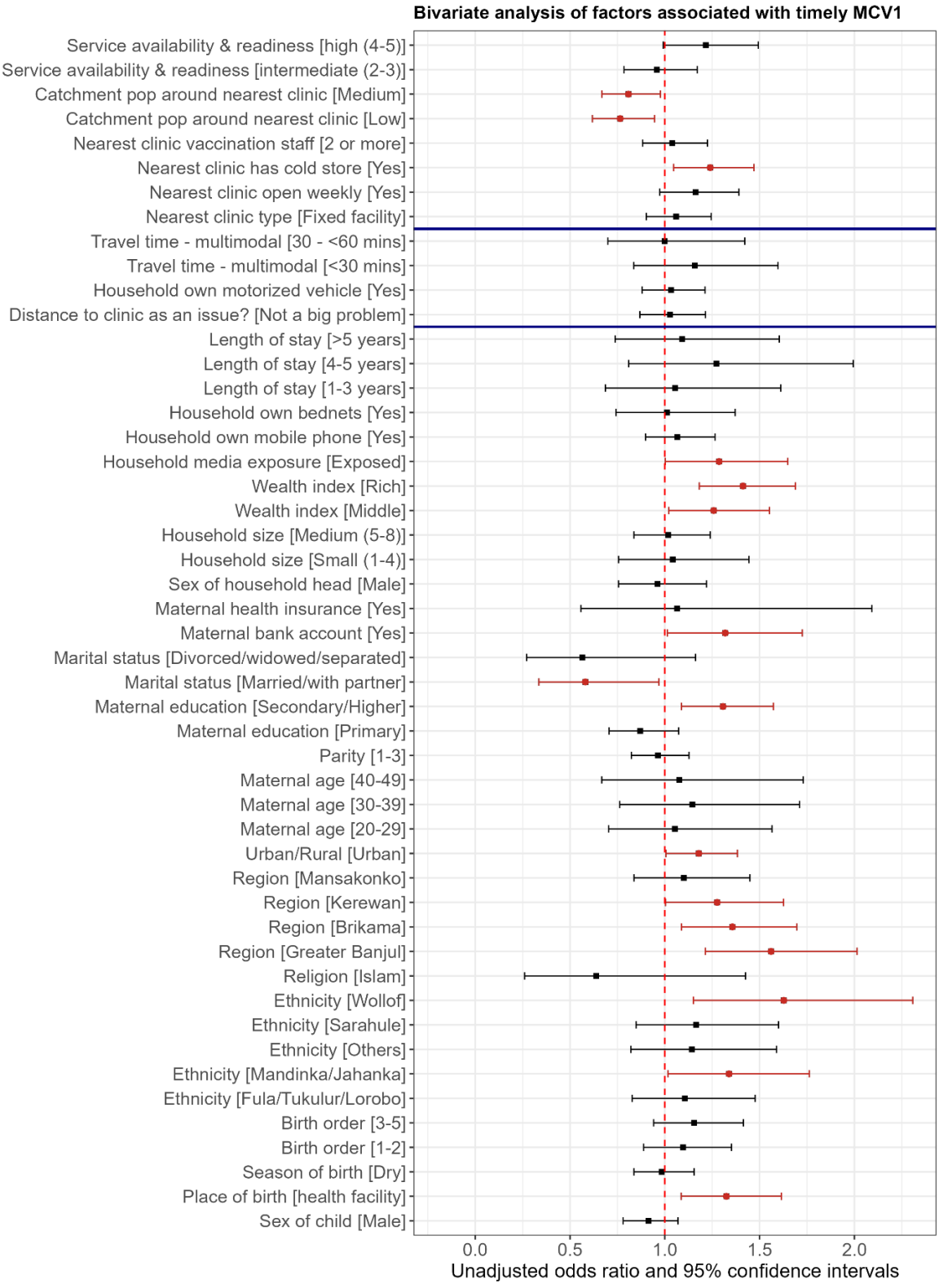


Fig S11: Unadjusted odds ratio and corresponding 95% credible interval plots for determinants of timely first-dose of measles-containing vaccine (MCV1). Note: The vertical dashed red lines mark the odds ratio of 1. Red dots and lines show the aORs and 95CIs of variables that have significant associations with vaccination. Dark blue horizontal line separates the covariates in level 1, 2 and 3 factors.

References

1. Gambia Bureau of Statistics (GBoS) and ICF. The Gambia Demographic and Health Survey 2019-20. Banjul, The Gambia and Rockville, Maryland, USA, 2021.
2. The DHS Program - Gambia: Standard DHS, 2019.
3. World Health Organization. Harmonizing vaccination coverage measures in household surveys: A primer. Geneva, Switzerland: WHO, 2019.
4. World Bank Group. The Gambia: historical climate data. 2023. https://climateknowledgeportal.worldbank.org/country/gambia/climate-data-historical#:~:text=The%20Gambia%20experiences%20a%20Sahelian,season%20(June%20to%20October). (accessed 05 December 2023).
5. Wariri O, Utazi CE, Okomo U, et al. Mapping the timeliness of routine childhood vaccination in The Gambia: A spatial modelling study. *Vaccine* 2023.
6. McLafferty SL. GIS and Health Care. *Annual Review of Public Health* 2003; **24**(1): 25-42.
7. Ray N, Ebener S. AccessMod 3.0: computing geographic coverage and accessibility to health care services using anisotropic movement of patients. *International Journal of Health Geographics* 2008; **7**(1): 63.
8. Dotse-Gborgbortsi W, Tatem AJ, Alegana V, Utazi CE, Ruktanonchai CW, Wright J. Spatial inequalities in skilled attendance at birth in Ghana: a multilevel analysis integrating health facility databases with household survey data. *Tropical Medicine & International Health* 2020: tmi.13460-tmi.
9. Wariri O, Onuwabuchi E, Alhassan JAK, et al. The influence of travel time to health facilities on stillbirths: A geospatial case-control analysis of facility-based data in Gombe, Nigeria. *PLOS ONE* 2021; **16**(1): e0245297.
10. Alegana VA, Wright JA, Pentrina U, Noor AM, Snow RW, Atkinson PM. Spatial modelling of healthcare utilisation for treatment of fever in Namibia. *International Journal of Health Geographics* 2012; **11**(1): 6.
11. Joseph NK, Macharia PM, Ouma PO, et al. Spatial access inequities and childhood immunisation uptake in Kenya. *BMC Public Health* 2020; **20**(1): 1407.
12. Zanaga D, Van, De Kerchove, R., De Keersmaecker, W., Souverijns, N., Brockmann, C., Quast, R., Wevers, J., Grosu, A., Paccini, A., Vergnaud, S., Cartus, O., Santoro, M., Fritz, S., Georgieva, I., Lesiv, M., Carter, S., Herold, M., Li, Linlin, Tsendbazar, N.E., Ramoino, F., Arino, O. ESA WorldCover 10 m 2020 v100. In: European Space Agency, editor.; 2021.
13. OpenStreetMap Contributors. Open geospatial map data. 2023. : https://www.openstreetmap.org/ (accessed 29 January 2023).
14. DIVA-GIS. Download data by country: The Gambia. 2023. https://www.diva-gis.org/datadown (accessed 29 January 2023).
15. Dotse-Gborgbortsi W, Tatem AJ, Matthews Z, Alegana VA, Ofosu A, Wright JA. Quality of maternal healthcare and travel time influence birthing service utilisation in Ghanaian health facilities: a geographical analysis of routine health data. *BMJ Open* 2023; **13**(1): e066792.
16. van Duinen AJ, Adde HA, Fredin O, et al. Travel time and perinatal mortality after emergency caesarean sections: an evaluation of the 2-hour proximity indicator in Sierra Leone. *BMJ Global Health* 2020; **5**(12): e003943.
17. Tobler W. Three Presentations on Geographical Analysis and Modeling: Non- Isotropic Modeling; Speculations on the Geometry of Geography; and Global Spatial Analysis. Santa Barbara: University of California, 1993.
18. Burgert CR, Colston J, Roy T, Zachary B. Geographic displacement procedure and georeferenced data release policy for the Demographic and Health Surveys: Icf International; 2013.
19. Browne WJ, Subramanian SV, Jones K, Goldstein H. Variance partitioning in multilevel logistic models that exhibit overdispersion. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2005; **168**(3): 599-613.

Appendix 11: Ethical approval (LSHTM)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Oghenebrume Wariri
LSHTM

20 January 2021

Dear Dr Wariri

Study Title: Evaluating the contribution of sociodemographic characteristics and geographic access to immunization service points on timeliness and delays of infant vaccinations in The Gambia

LSHTM Ethics Ref: 22786

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Other	TRREE_GCP_WARIRI	22/11/2019	1
Investigator CV	Wariri_CV_30.10.2020	30/10/2020	1
Protocol / Proposal	Proposal_SCC	02/11/2020	1.0
Information Sheet	Explanatory note	03/11/2020	1.0
Investigator CV	CV BK 2020 4 pages	06/11/2020	1
Investigator CV	grundy-cv-2020	09/11/2020	1
Protocol / Proposal	Proposal_SCC_v2	07/12/2020	1.1
Covering Letter	Cover letter	07/12/2020	1
Investigator CV	Malick Sogur_CV_2020	09/12/2020	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

Appendix 12: Ethical approval (MRC Unit The Gambia at LSHTM)

The Gambia Government/MRC Joint
ETHICS COMMITTEE

C/o MRC Unit: The Gambia @ LSHTM, Fajara
P.O. Box 273, Banjul
The Gambia, West Africa
Fax: +220 – 4495919 or 4496513
Tel: +220 – 4495442-6 Ext. 2308
Email: ethics@mrc.gm

Dr Oghenebrume Wariri

MRCG at LSHTM, Fajara

18 January 2021

Dear Dr Wariri

Study Title: Evaluating the contribution of sociodemographic characteristics and geographic access to immunization service points on timeliness and delays of infant vaccinations in The Gambia

Project ID/ethics ref: 22786

Thank you for submitting your application which was considered by the Gambia Government/MRCG Joint Ethics Committee at its meeting held on 21 December 2020.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form and supporting documentation.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	TRREE_GCP_WARIRI	22/11/2019	1.0
Investigator CV	Wariri_CV_30.10.2020	30/10/2020	1.0
Protocol / Proposal	Proposal_SCC	02/11/2020	1.0
Information Sheet	Explanatory note	03/11/2020	1.0
Investigator CV	CV BK 2020 4 pages	06/11/2020	1.0
Investigator CV	grundy-cv-2020	09/11/2020	1.0
Protocol / Proposal	Proposal_SCC_v2	07/12/2020	1.1
Covering Letter	Cover letter	07/12/2020	1.0
Investigator CV	Malick Sogur_CV_2020	09/12/2020	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the Ethics Committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the Committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form. An annual report should be submitted to the Committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study. At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Additional information is available at: www.lshtm.ac.uk/ethics.

With best wishes

Yours sincerely

[redacted]

Dr Mohammadou Kabir Cham
Chairperson, Gambia Government/MRCG Joint Ethics Committee

C/O MRC Unit The Gambia at LSHTM
PO Box 273 Banjul, The Gambia
West Africa
Switchboard (+220) 4495442/6 Ext 2308
Fax (+220) 4495919/4496513
E-mail: ethics@mrc.gm
Intranet: http://mrcportal/Committees/SCC/SitePages/Home.aspx
Webpage:https://mrcportal.mrc.gm/Committees/SCC/SitePages/Home.aspx

Appendix 13: Links to R Codes developed for data cleaning, wrangling and analysis

Objective 2: https://github.com/drwariri/Mapping-the-timeliness-of-routine-childhood-vaccination-in-The-Gambia-a-spatial-modelling-study

Objective 3: https://github.com/drwariri/Impact-of-COVID-19-pandemic-on-the-timeliness-and-coverage-of-childhood-vaccination-in-The-Gambia

Objective 4: https://github.com/drwariri/Multi-level-determinants-of-timely-routine-childhood-vaccinations-in-The-Gambia