Title

The Impact of the COVID-19 Pandemic on Neonatal Health Outcomes in Sub-Saharan Africa: A Targeted Investigation of Medical Records in Kinshasa, Democratic Republic of the Congo with an Expansive Meta-Analysis among Sub-Saharan Countries

Author

Arena, Patrick Joseph

Publication Date

2023

UNIVERSITY OF CALIFORNIA

Los Angeles

The Impact of the COVID-19 Pandemic on Neonatal Health Outcomes in Sub-Saharan Africa: A Targeted Investigation of Medical Records in Kinshasa, Democratic Republic of the Congo with an Expansive Meta-Analysis among Sub-Saharan Countries

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

by

Patrick Joseph Arena

2023

ABSTRACT OF THE DISSERTATION

The Impact of the COVID-19 Pandemic on Neonatal Health Outcomes in Sub-Saharan Africa: A Targeted Investigation of Medical Records in Kinshasa, Democratic Republic of the Congo with an Expansive Meta-Analysis among Sub-Saharan Countries

by

Patrick Joseph Arena
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2023
Professor Anne W. Rimoin, Chair

Despite advances in maternal and neonatal health over the past few decades, a disproportionate amount of adverse birth outcomes (e.g., stillbirth, low birth weight [LBW], and preterm birth [PTB]) still occur in low- and middle-income countries. In the Democratic Republic of the Congo (DRC), health officials have been exploring ways to expand pharmacovigilance (PV) capabilities for the detection of adverse maternal and neonatal health outcomes and also striving to learn more about the impact of the COVID-19 pandemic on neonatal health outcomes. In response, this dissertation utilized a PV study – conducted from July 1, 2019 to January 31, 2021 in Kinshasa, DRC – in conjunction with external surveillance data and data from the literature to address these subjects. Chapter 1 provides a broad summary of the current state of maternal and neonatal health both generally and in the context of the DRC. Chapter 2 assesses the equivalency of alternative data sources (in the form of archival medical records and enhanced monitoring data) to external surveillance data for the detection of maternal and neonatal health outcomes; the results generally indicated that such alternative data sources could serve as suitable PV tools for the monitoring of adverse birth outcomes in Kinshasa, DRC. Chapter 3 utilizes natural experimental methods to investigate the impact of the COVID-19 pandemic on selected neonatal health outcomes; the results revealed that the stillbirth rate appeared to remain stable while the LBW and PTB rates seemed to decline slightly after the imposition of COVID-19 mitigation measures in Kinshasa, DRC. Chapter 4 employs systematic review and meta-analysis methodology to examine the relationship between COVID-19 mitigation measures and neonatal health outcomes in sub-Saharan Africa; despite issues concerning high heterogeneity, the results generally suggested no change in stillbirth, LBW, or PTB after the imposition of COVID-19 mitigation measures among multi-national/national/regional studies but also highlighted the need for further research within sub-Saharan African countries. Chapter 5 provides a high-level summary and implications for future research and public health. Overall, this dissertation provides insights on solutions for PV systems strengthening for the benefit of maternal and neonatal health outcomes and offers additional perspectives on the impact of the COVID-19 pandemic on neonatal health outcomes within the context of the DRC specifically and sub-Saharan Africa more generally.

The dissertation of Patrick Joseph Arena is approved.

Thomas R. Belin

Christie Yonghae Jeon

Roch Arnaud Kibsa Nianogo

Karin Nielsen

Anne W. Rimoin, Committee Chair

University of California, Los Angeles

2023

DEDICATION

To my family and friends, I would not be where I am today without you in my life. Thank you for all the love and support you have shown me throughout the years.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

First, I would like to thank my advisor and committee chair, Anne Rimoin, for welcoming me into the UCLA-DRC community and enabling me to become a well-versed epidemiologist. Through her guidance and encouragement over the course of the program, I was able to contribute to the COVID-19 response at UCLA, collaborate with the US FDA to strengthen pharmacovigilance capabilities in the DRC, and become an overall better researcher and public health practitioner; these experiences will forever shape my career trajectory, and I will always be thankful for them.

To the rest of my committee –Thomas Belin, Christie Jeon, Roch Nianogo, and Karin Nielsen – thank you for your guidance and support throughout this process. It was a great pleasure working through specific problems and discussing epidemiologic and biostatistical concepts with you all in the pursuit of my degree.

Thank you also to the UCLA-DRC Pharmacovigilance team – Nicole Hoff, Adva Gadoth, Dalau Mukadi Nkamba, Didine Kaba, Camille Dzogang, David Kampilu, and Michael Beia – as well as our FDA colleagues for accepting me onto the team and teaching me valuable lessons in research practice that I will never forget. And to the entire UCLA-DRC staff both in LA and Kinshasa, thank you for all your work that makes our research possible.

I would also like to thank all the great people I have met throughout my time at UCLA, such as Joy Miller, Marjan Javanbakht, Julia Heck, Jane Bandak, George Dewey, Alex Moran, and Angie Barrall, who have helped me in ways both large and small.

To my parents, Joseph and MaryAnn Arena, as well as my entire family, thank you for encouraging me and supporting me throughout my entire life and setting me up to be able to achieve this goal. It would not have been possible without you.

And lastly, a special thank you to my fiancée, Kate Kendle, for keeping me sane throughout the program and going above and beyond to keep us afloat while I completed the dissertation. I can never thank you enough for all your love and patience.

VITA

May 2014	Bachelor of Science, Biology Boston College Chestnut Hill, MA
Jul 2015 – Feb 2016	Assistant Regional Monitoring and Evaluation Manager Helen Keller International Phnom Penh, Cambodia
May 2016	Master of Public Health, Epidemiology Certificate in Global Health Columbia University New York, NY
Jun 2016 – Dec 2021	Study Coordinator Pfizer, Inc. New York, NY
Sep 2019	Opportunity Award University of California, Los Angeles Los Angeles, CA
Sep 2019 – Dec 2022	Graduate Student Researcher/Volunteer Researcher University of California, Los Angeles Los Angeles, CA
May 2020 – Sep 2020	Graduate Summer Research Mentorship Fellowship University of California, Los Angeles Los Angeles, CA
Jan 2021 – Jun 2023	Teaching Assistant/Associate University of California, Los Angeles Los Angeles, CA
Feb 2021	Student Service Award (Department of Epidemiology) University of California, Los Angeles Los Angeles, CA
Jun 2022 – Jun 2023	PhD Consultant Aetion, Inc. El Segundo, CA

Arena PJ, Dzogang C, Gadoth A, Nkamba DM, Hoff NA, Kampilu D, Beia M, Wong H-L, Anderson SA, Kaba D, Rimoin AW. Comparison of adverse pregnancy and birth outcomes using archival medical records before and during the first wave of the COVID-19 pandemic in Kinshasa, Democratic Republic of Congo: a facility-based, retrospective cohort study. BMC Pregnancy Childbirth. 2023;23(1):31. doi:10.1186/s12884-022-05291-w

Arena PJ, Huang K, Löfling L, Bahmanyar S, Mo J, Schachterle SE, Nunes AP, Smits E, Juuti R, Hoti F, Korhonen P, Adelborg K, Sundbøll J, Rasmussen TR, Løkke A, Ehrenstein V. Validation of safety outcomes in routinely collected data: lessons learned from a multinational post-approval safety study. Pharmacoepidemiol Drug Saf. 2022;10.1002/pds.5582. doi:10.1002/pds.5582

Jaksa A, **Arena PJ**, Chan KKW, Ben-Joseph RH, Jónsson P, Campbell UB. Transferability of real-world data across borders for regulatory and health technology assessment decision-making. Front Med (Lausanne). 2022;9:1073678. doi:10.3389/fmed.2022.1073678

Nkamba DM, **Arena PJ,** Gadoth A, Hoff NA, Dzogang C, Kampilu D, Beya M, Wong H-L, Anderson SA, Kaba D, Rimoin AW. Adherence to face mask use during the COVID-19 pandemic among women seeking antenatal care in Kinshasa, Democratic Republic of Congo. BMJ Open 2022;12:e060929. doi: 10.1136/bmjopen-2022-060929

Gadoth A, Nkamba DM, **Arena PJ,** Hoff NA, Dzogang C, Kampilu D, Beya M, Wong H-L, Anderson SA, Kaba D, Rimoin AW. Assessing the feasibility of passive surveillance for maternal immunization safety utilizing archival medical records in Kinshasa, Democratic Republic of Congo. Vaccine. 2022;40(26):3605-3613. doi:10.1016/j.vaccine.2022.04.073

Arena PJ, Mo J, Liu Q, Zhou X, Shen R, Gong R, Wentworth C, Murugesan S, Huang K. The incidence of acute myocardial infarction after elective spinal fusions or joint replacement surgery in the United States: a large-scale retrospective observational cohort study in 322,585 patients. Patient Saf Surg. 2021;15(1):30. doi:10.1186/s13037-021-00305-6

Arena PJ, Mo J, Sabharwal C, Begier E, Zhou X, Gurtman A, Liu Q, Shen R, Wentworth C, Huang K. The incidence of stroke among selected patients undergoing elective posterior lumbar fusion: a retrospective cohort study. BMC Musculoskelet Disord. 2020;21(1):612. Published 2020 Sep 14. doi:10.1186/s12891-020-03631-5

Arena PJ, Malta M, Rimoin AW, Strathdee SA. Race, COVID-19 and deaths of despair. EClinicalMedicine. 2020;25:100485. doi:10.1016/j.eclinm.2020.100485

Huang K, Tao S, Zhou X, Mo J, Zhu B, Shen P, Lin H, **Arena PJ**, He N. Incidence rates of health outcomes of interest among Chinese children exposed to selected vaccines in Yinzhou Electronic Health Records: A population-based retrospective cohort study. Vaccine. 2020;38(18):3422-3428. doi:10.1016/j.vaccine.2020.03.013

Chapter 1. Introduction

1.1. Neonatal Health

Despite advances in maternal and neonatal health over the past few decades, approximately 2.4 million children died during their first month of life in 2019 globally; moreover, there were about 6,700 newborn deaths every day, accounting for 47% of all child deaths under the age of five years (an increase from 40% of all child deaths under the age of five years in 1990).[1] According to the World Health Organization (WHO), preterm birth (PTB), intrapartum-related complications (i.e., birth asphyxia or lack of breathing at birth), neonatal infections, and congenital birth defects were the primary causes of neonatal death in 2017; however, the WHO noted that babies who had low birth weight (LBW) or were born to an HIV-infected mother were also at increased risk of mortality.[1] Additionally, the WHO estimates that there are nearly 2 million stillbirths every year, of which 98% occur in low- and middle-income countries (LMICs),[2] which are defined as countries with a gross national income per capita of $13,205 or less by the World Bank.[3] In terms of global distribution, sub-Saharan Africa was estimated to have the world's highest neonatal mortality rate in 2019 with 27 deaths per 1,000 live births, followed by Central and Southern Asia with 24 deaths per 1,000 live births.[1] Likewise, a systematic assessment of global stillbirths from 2000 to 2019 concluded that sub-Saharan Africa had the highest stillbirth rate at 21.7 stillbirths per 1,000 total births in 2019.[4]

While neonatal deaths and stillbirths are critical public health issues in and of themselves, the WHO and other health agencies also recognize that children who survive the neonatal period can still endure significant health challenges later in life as a result of PTB, LBW, and other complications suffered at birth. For example, LBW newborns have a higher risk of general morbidity, stunting in childhood, and long-term developmental problems; they are also more likely to develop adult-onset chronic conditions (e.g., cardiovascular disease).[5] Likewise, preterm infants can experience a variety of short- and long-term complications such as respiratory distress syndrome, cerebral palsy, feeding difficulties, dysplasia, and visual/hearing problems; PTB is also associated with significant costs to the healthcare system as well as psychological and financial hardship among families of preterm newborns.[6] As a result, these health challenges can have broader implications for the socioeconomic development of communities and countries worldwide; however, as was the case with neonatal mortality and stillbirth, complications like PTB and LBW are concentrated in LMICs,[5,6] thereby resulting in a disproportionate burden on the health systems and economies of these countries.

In response to this situation, a variety of programs aimed at improving maternal and child health have been launched by the WHO and other international organizations, such as the United Nations Children's Fund (UNICEF); one of the most prominent initiatives in this area is the Every Newborn Action Plan (ENAP), which "provides a road map of strategic actions for ending preventable newborn mortality and stillbirth and contributing to reducing maternal mortality and morbidity" until 2030.[7] The key tenets under ENAP and the general WHO/UNICEF strategy include ensuring the availability of essential medicines and commodities, improving participation in and quality of antenatal care, promoting the availability of skilled birth attendants/midwives, supporting an adequate hygiene infrastructure, developing competent and motivated staff, reducing inequities, and strengthening data systems.[1,7,8] Since ENAP's inception in 2014, there has been strong evidence of significant progress in improving maternal and neonatal health, but challenges still remain in ensuring that all countries reach their 2030 targets of ending preventable newborn deaths and ending preventable stillbirths.[8,9] Consequently, other public health tools, such as maternal immunization, may need to be utilized as additional ways to further improve maternal and neonatal health outcomes and thus help countries achieve their ENAP goals.

1.2. Pharmacovigilance

Maternal immunization – the practice of vaccinating women during their pregnancy – is a public health intervention aimed at boosting both maternal and infant humoral immune protection against a variety of vaccine-preventable diseases.[10–16] Currently, most infant immunizations are administered between six weeks and six months of age; additionally, several vaccines (e.g., diphtheria, tetanus, and pertussis vaccines) require multiple doses to confer full immunity. These factors create an "immunity gap" whereby infection-related hospitalizations and deaths are higher among neonates and young infants than in older children due to low levels of immune protection.[10] As infectious diseases remain a leading cause of death among children under five years of age,[17] maternal immunization offers an innovative means of protecting newborns when they are most vulnerable to infection – prior to immune system development and the completion of neonatal vaccination regimens – through the passive, transplacental transfer of maternal antibodies.[10,13]

Despite the increased use of maternal immunization strategies throughout the world though, its safety has only been evaluated in limited contexts and remains particularly understudied in LMICs, where a large number of vaccine-preventable diseases and other infection diseases remain endemic.[10,18,19] In order to better facilitate research into the safety of maternal immunization approaches both within and across countries, the Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) project created standardized guidelines and case definitions for the identification of maternal immunization and neonatal health outcomes.[20] However, to effectively utilize the GAIA criteria for safety surveillance, countries first need robust pharmacovigilance (PV) data systems for the detection of adverse events (AEs) associated with various drugs and vaccines. Although such systems are well established and continue to evolve in high-income countries (HICs), robust PV systems are lacking in LMICs.[21–24] For example, a recent investigation that conducted interviews with strategic leaders in national PV centers across eighteen African countries concluded that over-reliance on development partners, indifference of national governments to provide support, and lack of sustainable engagement with public health programs has prevented the establishment of strong national PV programs in their countries.[22] Consequently, maternal immunization programs can be hampered in LMICs due to the lack of suitable PV systems that would allow public health officials to confidently and effectively monitor its safety.

Given the current state of PV systems in LMICs, more research is needed to improve their ability to monitor maternal immunization programs and confirm that the practice is not associated with AEs (such as stillbirth, LBW, and PTB) among populations in LMICs. Thus, by enhancing PV capabilities in LMICs, such efforts would also indirectly improve maternal and neonatal health, thereby contributing to the attainment of ENAP targets. Furthermore, strengthening PV systems could have broader impacts on surveillance systems for other health issues, thereby enabling more effective monitoring and management of additional public health challenges in LMICs. Indeed, such advancements in monitoring abilities could even provide opportunities to examine the impact of the COVID-19 pandemic on maternal and neonatal health outcomes.

1.3. The COVID-19 Pandemic

Since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in December 2019, the COVID-19 pandemic has devastated health systems throughout the world and strained global health infrastructures.[25] For instance, the WHO estimates there have been approximately 760 million confirmed cases of COVID-19 (including nearly 7 million reported deaths) as of March 16, 2023.[26] In response to the rapid spread of SARS-CoV-2 throughout the first year of the pandemic, countries around the world enacted a variety of mitigation measures (e.g., lockdowns, school closures, mask mandates, etc.) to help curb the spread of the virus. Many feared that such measures would lead to decreased access to healthcare, particularly maternal and neonatal health services, as well as increased rates of adverse pregnancy and birth outcomes, especially within sub-Saharan African countries and other LMICs.[27–29] Indeed, some of the earliest investigations into the association between COVID-19 pandemic policies and maternal and neonatal health in LMICs (i.e., in South Africa,[30] Pakistan,[31] and Nepal[32]) suggested that lockdowns led to decreases in routine immunizations, institutional delivery rates, and/or the utilization of child healthcare services. Additionally, there were also concerns that the pandemic may have also negatively impacted pregnant women and their newborns via the negative consequences of stress associated with fear of the virus or the economic implications of lockdowns.[33–35]

Now more than three years into the pandemic, our overall comprehension regarding the global health impact of the COVID-19 pandemic on maternal and neonatal health outcomes is still evolving. Concerning the relationship between SARS-CoV-2 infection and neonatal health outcomes, the literature broadly supports an association between SARS-CoV-2 infection during pregnancy and certain adverse birth outcomes, such as PTB and stillbirth;[36–40] in fact, agencies like the United States Centers for Disease Control and Prevention (CDC) regularly advise that women who have COVID-19 during their pregnancy are “at increased risk” for both stillbirth and PTB.[40] However, there have been inconsistent results from a variety of studies regarding the impact of COVID-19 mitigation measures on maternal and neonatal health outcomes, thereby making it challenging to draw broad conclusions or generalize findings across populations.

For example, one of the first meta-analyses on this subject that compared outcomes before and during the first wave of the pandemic reported increases in only maternal deaths, stillbirth, ruptured ectopic pregnancies, and maternal depression (with no corresponding increases or decreases found for maternal gestational diabetes, LBW, PTB, or hypertensive disorders of pregnancy).[41] Nevertheless, later meta-analyses investigating this topic have reported conflicting results (i.e., some have found no changes in stillbirth during pandemic policy periods while others described decreases in PTB during such periods).[42–47] Although it would be assumed that any disruptions to the healthcare system would generally result in worse health outcomes, some researchers have posited that the overall reduction in infectious disease incidence, lessening of stress levels due to remote work, and decreased exposure to air pollution as a result of mitigation measures could contribute to potential declines in certain adverse birth outcomes, such as PTB.[47–49] Still though, others have argued that methodological issues (e.g., a small number of outcomes and uncontrolled confounding) as well as the possibility of publication bias undermine our ability to draw firm conclusions.[50,51]

Moreover, our understanding of any associations between the COVID-19 pandemic and maternal and neonatal health outcomes becomes even more muddled when we stratify by country economic status as various studies have suggested that pregnant women and their newborns in LMICs are potentially more vulnerable to certain adverse health outcomes compared to their counterparts in HICs as a result of the COVID-19 pandemic.[41,46,47] Either way though, the COVID-19 pandemic has certainly altered the maternal and neonatal health landscape in ways that are not yet fully understood but may have direct and indirect impacts on populations from both HICs and LMICs. Therefore, more research is needed to comprehensively understand the impacts of the COVID-19 pandemic on maternal and neonatal health outcomes so that appropriate public health responses can be developed to address any short- and long-terms effects and to also support LMICs in achieving their ENAP targets; moreover, the COVID-19 pandemic represents an opportunity for researchers to examine the effects of mitigations measures on maternal and neonatal health outcomes so that public health officials can be better-prepared in case similar policies need to be introduced in response to future infectious disease outbreaks.

1.4. The Democratic Republic of the Congo

An emblematic LMIC that is currently facing challenges related to PV systems strengthening and the impact of the COVID-19 pandemic is the Democratic Republic of the Congo (DRC), which is a Francophone country located in Central Africa that is bordered by nine other countries (i.e., Angola, Burundi, Central African Republic, Republic of Congo, Rwanda, South Sudan, Tanzania, Uganda, and Zambia);[52] with an estimated population of 97 million in 2022, it is the fourth most-populous country in Africa and the second largest geographically.[53–55] The capital of the DRC is Kinshasa, which is one of the most populous cities in Africa with a population of approximately 15.6 million people;[54] additionally, almost half of the population (i.e., 44.5%) lives in urban areas.[56] The country is classified as a low-income economy by the World Bank and ranks among the five poorest nations in the world.[53,55,57] Though the DRC is rich in mineral resources (e.g., cobalt, gold, and copper), the lack of formal economic opportunities, a history of colonialism, political conflicts, and instability, and high rates of malnutrition and infectious diseases (e.g., malaria and measles) all contribute to its current economic situation.[58,59]

With regards to neonatal health outcomes, the DRC had the fifth highest number of newborn deaths in the world in 2019 behind India, Nigeria, Pakistan, and Ethiopia.[1] The stillbirth rate in the DRC is also especially high. For instance, a recent systematic assessment of the global burden of stillbirth determined that the global rate was 13.9 stillbirths per 1000 total births;

however, the national stillbirth rate in the DRC was estimated to be almost twice the global rate (i.e., 27.2 stillbirths per 1000 total births).[4] Likewise, newborns in the DRC are at an increased risk for LBW and PTB compared to newborns born in HICs. For example, a systematic analysis of global LBW trends found that the national LBW prevalence in the DRC was 10.8% in 2015, a prevalence higher than that reported for North America, Europe, Australia, and New Zealand (i.e., 7.0%).[5] Similarly, a systematic review and modelling analysis of the global prevalence of PTB determined that the national PTB prevalence in the DRC was 9.8% and that preterm newborns in DRC represented 2.1% of the global PTB burden.[6] Thus, the DRC represents an area with a high burden of neonatal morbidity and mortality; as a result, the DRC has been identified as a priority country within the ENAP framework.[7,8]

Although these poor neonatal health metrics may suggest a dysfunctional overall health system in the DRC, the country has in fact made recent strides in other areas, including PV. For example, the DRC recently established a national PV center, located at the University of Kinshasa within the Unit of Clinical Pharmacology and Pharmacovigilance, in 2009 after a recommendation by the WHO.[60] As a result, a variety of PV investigations have been performed in the country over the past few years.[60–64] Indeed, since the creation of the national PV center, DRC has been one of the most active contributors in Africa to VigiBase, which is the WHO's global individual case safety reports database.[60] Nonetheless, a number of challenges still face the national PV system in the DRC; more specifically, Nzolo et al. have highlighted inconsistent funding, poor implementation of regional PV centers, weak collaborations with healthcare providers, and delayed data collection mechanisms as key barriers to the system's long-term success.[60] Steady funding streams and novel solutions to improve data collection are therefore urgently needed to strengthen the national PV system and its ability to detect AEs (including ones that are of particular interest to maternal and neonatal health, like stillbirth, LBW, and PTB); additionally, advancements in data collection abilities could also have synergistic effects on the general surveillance infrastructure and thus allow for the examination of the impact of the COVID-19 pandemic on maternal and neonatal health outcomes in the DRC.

Another threat to population health, the COVID-19 pandemic has resulted in 95,814 confirmed cases with 1,464 associated deaths in the DRC as of March 16, 2023.[65] Despite the pandemic's ubiquity over the past three years, limited research has been conducted on the effect of the pandemic (including pandemic policy measures) on maternal and neonatal health outcomes in the DRC; for example, a case report describing one of the country's first pregnant women diagnosed with COVID-19 was not published until January 2021 (i.e., almost one year after the start of the pandemic).[66] Additionally, most investigations have focused on the pandemic's impact on maternal and neonatal health services as opposed to health outcomes. For example, an interrupted time series (ITS) analysis using health information management system data during the first wave of the pandemic in Kinshasa found that maternal health services and vaccinations were not significantly affected by the pandemic itself or by lockdown measures.[67] Moreover, research from eight sub-Saharan African countries (including the DRC) indicated that the most substantial reductions in medical services during the early stages of the pandemic were reported for outpatient consultations and childhood vaccinations, while results for reproductive and maternal healthcare service utilization were mixed.[68] Though one study by Naqvi et al.[69] did investigate maternal and neonatal health outcomes in six LMICs (including the DRC) and reported no increases in stillbirth, neonatal mortality, maternal mortality, LBW, or PTB during the COVID-19 period compared with the previous year, this analysis did not provide country-specific information for the DRC; instead, the authors grouped the DRC together with Zambia and Kenya (into an "Africa" category), thereby making it difficult to determine the pandemic's effect in the DRC specifically.[69]

Thus, our understanding of the impact of COVID-19 on neonatal health outcomes in the DRC is very limited. However, this knowledge gap extends to the rest of the continent as only a few studies have been conducted on the subject within sub-Saharan Africa. For instance, a living systematic review and meta-analysis on the association between the COVID-19 pandemic and pregnancy/neonatal outcomes identified over fifty studies that analyzed stillbirth, LBW, PTB, neonatal mortality, and maternal mortality,[45] yet only three of these studies (i.e., Caniglia et al.,[48] Kassie et al.,[70] and Shakespeare et al.[71]) were conducted in sub-Saharan African countries (i.e., Botswana, Ethiopia, and Zimbabwe, respectively). Consequently, more research on this subject within both sub-Saharan Africa generally and the DRC specifically is necessary in order to provide critical health information for the region and further the global dialogue in this area of research.

1.5. Dissertation Rationale

Although PV system strengthening for the improvement of neonatal health and the COVID-19 pandemic's association with neonatal health outcomes in LMICs are not inherently related topics, our research group was in a unique position to address them both through a PV study – conducted from July 1, 2019 to January 31, 2021 in Kinshasa, DRC – that was originally designed to assess the utility of archival medical records and enhanced monitoring data for the detection of adverse birth outcomes in the context of maternal immunization. Early results into the feasibility of these archival medical records and enhanced monitoring data as potential PV tools have already been published and have generally shown that these data could feasibly be utilized to screen for and identify a variety of pregnancy and birth outcomes, such as stillbirth, PTB, LBW, small for gestational age, and congenital microcephaly (despite some issues associated with interfacility variability).[14–16] However, further research can be done with these data by assessing their equivalency to other data sources frequently used for surveillance purposes in the DRC in order to confirm that they are accurately capturing the outcomes of interest, thereby further justifying their use for PV purposes. Additionally, the archival medical records can be employed to gain more insight into potential associations between the COVID-19 pandemic and selected neonatal health outcomes (i.e., stillbirth, LBW, and PTB) in Kinshasa; lastly, utilization of existing data in the literature can serve to augment the results found for the COVID-19 pandemic's impact on stillbirth, LBW, and PTB in the DRC and examine any such association throughout sub-Saharan Africa.

Therefore, this dissertation aimed to address three main topics: 1) PV system strengthening in Kinshasa, DRC; 2) the association between the COVID-19 pandemic and selected neonatal health outcomes in Kinshasa, DRC; and 3) the association between the COVID-19 pandemic and selected neonatal health outcomes in sub-Saharan Africa. With regards to PV system strengthening in the DRC, archival medical records and enhanced monitoring data represent innovative means to enable surveillance of AEs in a manner similar to the use of electronic health records and active surveillance tools in HICs; however, it is first necessary to ensure that these data produce valid prevalence estimates of key outcomes by comparing such estimates to those from an external data source frequently used for surveillance purposes in the DRC. Moreover, due to the nature of the data collection period for the archival medical records, these data can also be used to investigate the association between the COVID-19 pandemic and selected neonatal health outcomes in Kinshasa by comparing the period immediately prior to the onset of the COVID-19 pandemic to the COVID-19 mitigation measures period via natural experimental methods. Lastly, data from the relevant literature combined with the data from Kinshasa can be collected and summarized using meta-analytic methods to further our understanding of the association between COVID-19 pandemic policies and selected neonatal health outcomes in sub-Saharan Africa. Thus, the three specific aims of this dissertation (which correspond to the next three chapters) are the following:

1. To conduct an equivalence analysis comparing the prevalence of selected maternal and neonatal health outcomes found using both archival medical records and enhanced monitoring data to the prevalence of the same outcomes identified using an external surveillance data source in Kinshasa, DRC;
2. To investigate the impact of the COVID-19 pandemic on selected neonatal health outcomes in Kinshasa, DRC by comparing the rates of stillbirth, LBW, and PTB between the pre-COVID-19 period and the COVID-19 mitigation measures period via ITS methodology; and
3. To perform a systematic review and meta-analysis regarding the relationship between COVID-19 mitigation measures and stillbirth, LBW, and PTB in sub-Saharan Africa in order to better contextualize both the results found for Kinshasa, DRC as well as the broader situation within sub-Saharan Africa.

1.6. References

1. World Health Organization. Newborns: improving survival and well-being. Published September 19, 2020. Accessed May 2, 2023. https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality

2. World Health Organization. Stillbirth. Accessed May 2, 2023. https://www.who.int/health-topics/stillbirth

3. World Bank. World Bank Country and Lending Groups – World Bank Data Help Desk. World Bank Data. Accessed April 24, 2023. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

4. Hug L, You D, Blencowe H, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. *The Lancet*. 2021;398(10302):772-785. doi:10.1016/S0140-6736(21)01112-0

5. Blencowe H, Krasevec J, Onis M de, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. 2019;7(7):e849-e860. doi:10.1016/S2214-109X(18)30565-5

6. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0

7. World Health Organization. Every Newborn Action Plan. Accessed May 2, 2023. https://www.who.int/initiatives/every-newborn-action-plan

8. World Health Organization, United Nations Children's Fund (UNICEF). *Every Newborn Progress Report 2019.*; 2020. Accessed May 2, 2023. https://www.healthynewbornnetwork.org/resource/every-newborn-progress-report-2019-2/

9. Syed U, Kinney MV, Pestvenidze E, et al. Advancing maternal and perinatal health in low- and middle-income countries: A multi-country review of policies and programmes. *Front Glob Womens Health*. 2022;3. Accessed May 2, 2023. https://www.frontiersin.org/articles/10.3389/fgwh.2022.909991

10. Omer SB. Maternal Immunization. *N Engl J Med*. 2017;376(13):1256-1267. doi:10.1056/nejmra1509044

11. Engmann C, Fleming JA, Khan S, et al. Closer and closer? Maternal immunization: current promise, future horizons. *J Perinatol*. 2020;40(6):844-857. doi:10.1038/s41372-020-0668-3

12. World Health Organization. *Maternal Immunization and Antenatal Care Service Delivery Situation Analysis: Report of the MIACSA Project, 2016-2019*. World Health Organization; 2020. https://www.who.int/publications/i/item/9789240004016

13. Niewiesk S. Maternal Antibodies: Clinical Significance, Mechanism of Interference with Immune Responses, and Possible Vaccination Strategies. *Front Immunol*. 2014;5. Accessed May 2, 2023. https://www.frontiersin.org/articles/10.3389/fimmu.2014.00446

14. Arena PJ, Dzogang C, Gadoth A, et al. Comparison of adverse pregnancy and birth outcomes using archival medical records before and during the first wave of the COVID-19 pandemic in Kinshasa, Democratic Republic of Congo: a facility-based, retrospective cohort study. *BMC Pregnancy Childbirth*. 2023;23(1):31. doi:10.1186/s12884-022-05291-w

15. Gadoth A, Mukadi Nkamba D, Arena PJ, et al. Assessing the feasibility of passive surveillance for maternal immunization safety utilizing archival medical records in Kinshasa, Democratic Republic of the Congo. *Vaccine*. 2022;40(26):3605-3613. doi:10.1016/j.vaccine.2022.04.073

16. Arena PJ, Gadoth A, Nkamba DM, et al. Prospective assessment of pregnancy and birth outcomes using the Global Alignment of Immunization Safety Assessment in pregnancy criteria in Kinshasa, Democratic Republic of the Congo. *BMJ Public Health - Rev*. Published online 2023.

17. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). *Levels & Trends in Child Mortality: Report 2019, Estimates Developed by the United Nations Inter-Agency Group for Child Mortality Estimation*. United Nations Children's Fund; 2019. https://www.unicef.org/reports/levels-and-trends-child-mortality-report-2019

18. Stuurman AL, Riera M, Lamprianou S, et al. Vaccine safety surveillance in pregnancy in low- and middle-income countries using GAIA case definitions: A feasibility assessment. *Vaccine*. 2018;36(45):6736-6743. doi:10.1016/j.vaccine.2018.09.033

19. Stuurman AL, Sharan A, Jahagirdar S, et al. WHO global vaccine safety multi-country collaboration project on safety in pregnancy: Assessing the level of diagnostic certainty using standardized case definitions for perinatal and neonatal outcomes and maternal immunization. *Vaccine X*. 2021;9:100123. doi:10.1016/j.jvacx.2021.100123

20. Bonhoeffer J, Kochhar S, Hirschfeld S, et al. Global alignment of immunization safety assessment in pregnancy - The GAIA project. *Vaccine*. 2016;34(49):5993-5997. doi:10.1016/j.vaccine.2016.07.006

21. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. *Expert Rev Clin Pharmacol*. 2015;8(4):449-460. doi:10.1586/17512433.2015.1053391

22. Ampadu HH, Hoekman J, Arhinful D, Amoama-Dapaah M, Leufkens HGM, Dodoo ANO. Organizational capacities of national pharmacovigilance centres in Africa: assessment of resource elements associated with successful and unsuccessful pharmacovigilance experiences. *Glob Health*. 2018;14(1):109. doi:10.1186/s12992-018-0431-0

23. Elshafie S, Zaghloul I, Roberti AM. Pharmacovigilance in developing countries (part I): importance and challenges. *Int J Clin Pharm*. 2018;40(4):758-763. doi:10.1007/s11096-017-0570-z

24. Elshafie S, Roberti AM, Zaghloul I. Pharmacovigilance in developing countries (part II): a path forward. *Int J Clin Pharm*. 2018;40(4):764-768. doi:10.1007/s11096-017-0588-2

25. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. *Physiol Genomics*. 2020;52(11):549-557. doi:10.1152/physiolgenomics.00089.2020

26. World Health Organization. Global: WHO Coronavirus (COVID-19) Dashboard. Accessed March 16, 2023. https://covid19.who.int

27. Feyissa GT, Tolu LB, Ezeh A. Impact of COVID-19 Pandemic on Sexual and Reproductive Health and Mitigation Measures: The Case of Ethiopia. *Afr J Reprod Health*. 2020;24(s1):24-26. doi:10.29063/ajrh2020/v24i2s.3

28. Govender D, Naidoo S, Taylor M. Don't Let Sexual and Reproductive Health become Collateral Damage in the Face of the COVID-19 Pandemic: A Public Health Perspective. *Afr J Reprod Health*. 2020;24(s1):56-63. doi:10.29063/ajrh2020/v24i2s.9

29. Oyediran KA, Makinde OA, Adelakin O. The Role of Telemedicine in Addressing Access to Sexual and Reproductive Health Services in sub-Saharan Africa during the COVID-19 Pandemic. *Afr J Reprod Health*. 2020;24(s1):49-55. doi:10.29063/ajrh2020/v24i2s.8

30. Siedner MJ, Kraemer JD, Meyer MJ, et al. Access to primary healthcare during lockdown measures for COVID-19 in rural South Africa: an interrupted time series analysis. *BMJ Open*. 2020;10(10):e043763. doi:10.1136/bmjopen-2020-043763

31. Chandir S, Siddiqi DA, Setayesh H, Khan AJ. Impact of COVID-19 lockdown on routine immunisation in Karachi, Pakistan. *Lancet Glob Health*. 2020;8(9):e1118-e1120. doi:10.1016/S2214-109X(20)30290-4

32. KC A, Gurung R, Kinney MV, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. *Lancet Glob Health*. 2020;8(10):e1273-e1281. doi:10.1016/S2214-109X(20)30345-4

33. Abdoli A, Falahi S, Kenarkoohi A, Shams M, Mir H, Jahromi MAM. The COVID-19 pandemic, psychological stress during pregnancy, and risk of neurodevelopmental disorders in offspring: a neglected consequence. *J Psychosom Obstet Gynaecol*. 2020;41(3):247-248. doi:10.1080/0167482X.2020.1761321

34. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol*. 2020;222(6):521-531. doi:10.1016/j.ajog.2020.03.021

35. Saccone G, Florio A, Aiello F, et al. Psychological impact of coronavirus disease 2019 in pregnant women. *Am J Obstet Gynecol*. 2020;223(2):293-295. doi:10.1016/j.ajog.2020.05.003

36. Regan AK, Arah O, Fell DB, Sullivan SG. SARS-CoV-2 infection during pregnancy and associated perinatal health outcomes: a national US cohort study. *J Infect Dis*. Published online December 27, 2021:jiab626. doi:10.1093/infdis/jiab626

37. Gurol-Urganci I, Jardine JE, Carroll F, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. *Am J Obstet Gynecol*. 2021;225(5):522.e1-522.e11. doi:10.1016/j.ajog.2021.05.016

38. DeSisto CL, Wallace B, Simeone RM, et al. Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization - United States, March 2020-September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(47):1640-1645. doi:10.15585/mmwr.mm7047e1

39. Stock SJ, Carruthers J, Calvert C, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat Med*. 2022;28(3):504-512. doi:10.1038/s41591-021-01666-2

40. CDC. Pregnant and Recently Pregnant People. Centers for Disease Control and Prevention. Published December 17, 2021. Accessed March 19, 2023. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html

41. Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health*. 2021;9(6):e759-e772. doi:10.1016/S2214-109X(21)00079-6

42. Vaccaro C, Mahmoud F, Aboulatta L, Aloud B, Eltonsy S. The impact of COVID-19 first wave national lockdowns on perinatal outcomes: a rapid review and meta-analysis. *BMC Pregnancy Childbirth*. 2021;21(1):676. doi:10.1186/s12884-021-04156-y

43. Yao XD, Zhu LJ, Yin J, Wen J. Impacts of COVID-19 pandemic on preterm birth: a systematic review and meta-analysis. *Public Health*. 2022;213:127-134. doi:10.1016/j.puhe.2022.10.015

44. Hawco S, Rolnik DL, Woolner A, et al. The impact of mitigation measures on perinatal outcomes during the first nine months of the COVID-19 pandemic: A systematic review with meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2022;274:117-127. doi:10.1016/j.ejogrb.2022.05.007

45. Yang J, D'Souza R, Kharrat A, Fell DB, Snelgrove JW, Shah PS. COVID-19 pandemic and population-level pregnancy and neonatal outcomes in general population: A living systematic review and meta-analysis (Update#2: November 20, 2021). *Acta Obstet Gynecol Scand*. 2022;101(3):273-292. doi:10.1111/aogs.14318

46. Gajbhiye RK, Sawant MS, Kuppusamy P, et al. Differential impact of COVID-19 in pregnant women from high-income countries and low- to middle-income countries: A systematic review and meta-analysis. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet*. 2021;155(1):48-56. doi:10.1002/ijgo.13793

47. Calvert C, Brockway M (Merilee), Zoega H, et al. Changes in preterm birth and stillbirth during COVID-19 lockdowns in 26 countries. *Nat Hum Behav*. Published online February 27, 2023:1-16. doi:10.1038/s41562-023-01522-y

48. Caniglia EC, Magosi LE, Zash R, et al. Modest reduction in adverse birth outcomes following the COVID-19 lockdown. *Am J Obstet Gynecol*. 2021;224(6):615.e1-615.e12. doi:10.1016/j.ajog.2020.12.1198

49. Arun Babu T, Sharmila V, Vishnu Bhat B. Curious scenario of changes in incidence of preterm births during COVID-19 pandemic. Pointers for future research? *Eur J Obstet Gynecol Reprod Biol*. 2020;253:333-334. doi:10.1016/j.ejogrb.2020.08.055

50. Goldenberg RL, McClure EM. Have Coronavirus Disease 2019 (COVID-19) Community Lockdowns Reduced Preterm Birth Rates? *Obstet Gynecol*. 2021;137(3):399-402. doi:10.1097/AOG.0000000000004302

51. Sisti G, Joseph JT. Reduction in preterm birth rate during the COVID-19 pandemic: Analysing causation. *BJOG Int J Obstet Gynaecol*. 2023;130(3):285. doi:10.1111/1471-0528.17312

52. Payanzo N, Cordell DD, Wiese BM, Lemarchand R. Democratic Republic of the Congo. Encyclopedia Britannica. Published April 26, 2023. Accessed May 3, 2023. https://www.britannica.com/place/Democratic-Republic-of-the-Congo

53. World Bank. Democratic Republic of Congo. World Bank. Published March 29, 2023. Accessed May 3, 2023. https://www.worldbank.org/en/country/drc/overview

54. United Nations Department of Economic and Social Affairs Population Division. World Population Prospects 2022. Published 2022. Accessed May 3, 2023. https://population.un.org/wpp/

55. Barrall A. *ReKAP of the COVID-19 Pandemic: Knowledge, Attitudes, and Practices among Healthcare Workers with Varying Ebola History in the Democratic Republic of the Congo, August 2020 to August 2021*. UCLA; 2023. Accessed May 3, 2023. https://escholarship.org/uc/item/6r7263vk

56. Editors. Democratic Republic of the Congo Summary. Encyclopedia Britannica. Accessed May 3, 2023. https://www.britannica.com/summary/Democratic-Republic-of-the-Congo

57. World Bank. World Development Indicators | Data Catalog. Published March 2, 2023. Accessed May 3, 2023. https://datacatalog.worldbank.org/search/dataset/0037712/World-Development-Indicators

58. Learn facts about Democratic Republic of Congo and poverty. Opportunity International. Accessed May 3, 2023. https://opportunity.org/our-impact/where-we-work/the-democratic-republic-of-congo-facts-about-poverty

59. Sasidharan S, Dhillon HS. A Snapshot of Poverty, Diseases and war – the Democratic Republic of the Congo. *Disaster Med Public Health Prep*.:1-4. doi:10.1017/dmp.2021.227

60. Nzolo D, Kuemmerle A, Lula Y, et al. Development of a pharmacovigilance system in a resource-limited country: the experience of the Democratic Republic of Congo. *Ther Adv Drug Saf*. 2019;10:2042098619864853. doi:10.1177/2042098619864853

61. Nzolo D, Ntetani Aloni M, Mpiempie Ngamasata T, et al. Adverse events following immunization with oral poliovirus in Kinshasa, Democratic Republic of Congo: preliminary results. *Pathog Glob Health*. 2013;107(7):381-384. doi:10.1179/2047773213Y.0000000113

62. Nzolo D, Engo Biongo A, Kuemmerle A, et al. Safety profile of fractional dosing of the 17DD Yellow Fever Vaccine among males and females: Experience of a community-based pharmacovigilance in Kinshasa, DR Congo. *Vaccine*. 2018;36(41):6170-6182. doi:10.1016/j.vaccine.2018.08.052

63. Ntamabyaliro NY, Burri C, Nzolo DB, et al. Drug use in the management of uncomplicated malaria in public health facilities in the Democratic Republic of the Congo. *Malar J*. 2018;17:189. doi:10.1186/s12936-018-2332-3

64. Nzolo D, Anto F, Hailemariam S, et al. Central and Peripheral Nervous System Disorders Following Ivermectin Mass Administration: A Descriptive Study Based on the Democratic Republic of Congo Pharmacovigilance System. *Drugs - Real World Outcomes*. 2017;4(3):151-158. doi:10.1007/s40801-017-0110-0

65. World Health Organization. Democratic Republic of the Congo: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data. Accessed March 16, 2023. https://covid19.who.int

66. Birindwa EK, Mulumeoderhwa GM, Nyakio O, et al. A case study of the first pregnant woman with COVID-19 in Bukavu, eastern Democratic Republic of the Congo. *Matern Health Neonatol Perinatol*. 2021;7(1):6. doi:10.1186/s40748-021-00127-5

67. Hategeka C, Carter SE, Chenge FM, et al. Impact of the COVID-19 pandemic and response on the utilisation of health services in public facilities during the first wave in Kinshasa, the Democratic Republic of the Congo. *BMJ Glob Health*. 2021;6(7):e005955. doi:10.1136/bmjgh-2021-005955

68. Shapira G, Ahmed T, Drouard SHP, et al. Disruptions in maternal and child health service utilization during COVID-19: analysis from eight sub-Saharan African countries. *Health Policy Plan*. 2021;36(7):1140-1151. doi:10.1093/heapol/czab064

69. Naqvi S, Naqvi F, Saleem S, et al. Health Care in Pregnancy During the COVID-19 Pandemic and Pregnancy Outcomes in Six Low-and-Middle-Income Countries: Evidence from a Prospective, Observational Registry of the Global Network for Women's and Children's Health. *BJOG Int J Obstet Gynaecol*. Published online April 4, 2022. doi:10.1111/1471-0528.17175

70. Kassie A, Wale A, Yismaw W. Impact of Coronavirus Diseases-2019 (COVID-19) on Utilization and Outcome of Reproductive, Maternal, and Newborn Health Services at Governmental Health Facilities in South West Ethiopia, 2020: Comparative Cross-Sectional Study. *Int J Womens Health*. 2021;13:479-488. doi:10.2147/IJWH.S309096

71. Shakespeare C, Dube H, Moyo S, Ngwenya S. Resilience and vulnerability of maternity services in Zimbabwe: a comparative analysis of the effect of Covid-19 and lockdown control measures on maternal and perinatal outcomes, a single-centre cross-sectional study at Mpilo Central Hospital. *BMC Pregnancy Childbirth*. 2021;21(1):416. doi:10.1186/s12884-021-03884-5

Chapter 2. Comparison of Maternal and Neonatal Prevalence Estimates from Both Archival Medical Records and Enhanced Monitoring Data to Surveillance Data in Kinshasa, Democratic Republic of the Congo

2.1. Abstract

In the Democratic Republic of the Congo (DRC), pharmacovigilance (PV) programs rely on spontaneous reports to identify adverse events; to assess the suitability of alternative data for PV purposes, we compared prevalence estimates from both archival medical records and enhanced monitoring data to those from the District Health Information System 2 (DHIS2). This investigation was an observational study conducted from July 2019 to January 2021 in Kinshasa, DRC that contained a retrospective, a prospective, and a surveillance cohort comprised of pregnant women and their newborns identified from archival medical records, enhanced monitoring data, and DHIS2 data, respectively. The following outcome measures were analyzed: mothers under 20 years of age, stillbirth, low birth weight (LBW), and preterm birth (PTB). Prevalence estimates were produced and compared to determine equivalency between the retrospective/prospective cohorts and the surveillance cohort via the two one-sided test (TOST) procedure. The final sample size was 14,256, 2,472, and 216,788 deliveries for the retrospective, prospective, and surveillance cohorts, respectively. Adjusted prevalence comparisons revealed that the difference between the retrospective/prospective and surveillance cohorts was -7.93% to -5.65% for mothers under 20 years of age, 0.20% to 0.31% for stillbirth, 1.36% to 1.98% for LBW, and 3.61% to 5.92% for PTB. The TOST procedure revealed that only stillbirth and LBW were (consistently) statistically equivalent between both the retrospective/prospective and the surveillance cohorts. Our results suggested that these alternative data sources are suitable tools for adverse birth outcome monitoring in Kinshasa, though issues were identified surrounding maternal age measurement.

Nonetheless, literature comparisons and potential limitations with PTB measurement in the DHIS2 indicated that these alternative data might have better recorded PTB prevalence. Overall, we hope that these findings lead to the more widespread use of archival medical records/enhanced monitoring data for the improvement of PV capabilities in the DRC.

2.2. Introduction

Pharmacovigilance (PV), which is defined as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse events (AEs) or any other medicine-/vaccine-related problem" by the World Health Organization (WHO),[1] forms a key part of national healthcare infrastructures. Specific PV activities, such as the establishment of medicine and vaccine safety profiles and the generation of surveillance activities, serve to prevent AEs, promote patient safety, and improve overall quality of life.[2,3] Traditionally, PV systems have relied on spontaneous reporting mechanisms to assess the safety of therapies; however, the passive nature of spontaneous reporting has been shown to be an ineffective tool for complete surveillance of AEs due to the fact that it relies primarily on voluntary reporting by patients and/or healthcare workers.[2–4] As a result, modern PV systems have incorporated electronic health records (EHRs) to more actively monitor patient safety because these EHRs provide large, population-based databases that contain real-world data generated during the course of routine clinical care.[4,5] Nonetheless, despite the immense potential of these large EHR databases for PV purposes, they were not designed as research tools; rather, they were originally developed to improve patient care and strengthen recordkeeping capabilities.[6] Consequently, their data elements can be incorrectly classified, poorly specified, and/or missing, thereby leading to information and selection biases that can jeopardize the interpretation of study results.[5–7]

In the Democratic Republic of the Congo (DRC), a national PV center was recently established in 2009 after a recommendation by the WHO.[8] As a result, a variety of PV investigations have been performed in the country over the past few years.[8–12] For example, a community-based PV study was conducted to supplement poor spontaneous reporting and to stimulate AE following immunization (AEFI) reporting during a mass yellow fever immunization campaign in 2016 by organizing PV information sessions at churches and academic institutions in Kinshasa; this approach resulted in more than 4,000 AEFI reports and provided evidence of a suitable safety profile for fractional dosing of the yellow fever vaccine.[10] Moreover, a retrospective PV study described central and peripheral nervous system disorders that occurred after mass administration of ivermectin in the DRC from 2009 to 2013 using the WHO spontaneous reporting database (VigiBase), which receives AE reports from participating national PV centers.[12] Nonetheless, the vast majority of PV studies conducted in the DRC have relied on spontaneous reporting mechanisms; in order to substantially reduce the cost of PV activities and continue to grow PV capabilities within the country, Nzolo et al. have called for the use of “existing health information systems” and other innovative data sources to supplement current PV programs.[8]

Based on the experience of high-income countries (HICs), EHR databases would be an ideal information system to incorporate into the Congolese national PV system. However, EHRs have not been broadly implemented and/or utilized across sub-Saharan Africa;[13] in the DRC specifically, there has been “political will” to expand health information management domains and capitalize on experiences with the District Health Information System 2 (DHIS2) and some hospital EHR systems.[14] Until those EHR capabilities are more fully realized though, other data sources, such as paper medical records and active surveillance questionnaires, can be used to expand the capabilities of the Congolese PV system. We previously conducted an investigation into the feasibility of archival (paper) medical records and enhanced monitoring data (i.e., active surveillance questionnaires) across delivery facilities throughout Kinshasa for the detection of maternal and neonatal health outcomes in the context of maternal immunization; these studies ultimately determined that archival medical records and enhanced monitoring data could be feasibly used to monitor certain adverse birth outcomes, such as low birth weight (LBW) and preterm birth (PTB).[15–17] As is the case with EHRs though, these alternative data sources may have data elements that are incorrectly classified, poorly specified, and/or missing since they are reflective of real-world patient care.[5–7] It is therefore critical that the suitability of these archival medical records/enhanced monitoring data be further evaluated so that their utility as PV tools can be better scrutinized.

Thus, we compared selected prevalence estimates from both archival medical records and enhanced monitoring data to those from the DHIS2 – "an open source, web-based platform used as a health management information system" by over seventy low- and middle-income countries (LMICs) to document health facility data[18,19] – in order to assesses the suitability of the archival medical records and enhanced monitoring data. By assessing the equivalency of these data with the DHIS2 surveillance data (i.e., a reference standard in the DRC), we aimed to determine whether such data could be validly used as alternative and/or supplementary PV tools for the surveillance of maternal and neonatal health outcomes in Kinshasa, DRC.

2.3. Methods

Study design

This investigation was an observational study that contained three cohorts: 1) a facility-based retrospective cohort, which included the pregnant women and their newborns identified from the archival medical records; 2) a facility-based prospective cohort, which included the pregnant women and their newborns identified from the enhanced monitoring data; and 3) a surveillance cohort, which included the pregnant women and their newborns identified from the DHIS2 surveillance data. The overall study site selection, study procedures, and variable descriptions for the retrospective and prospective cohorts have been described elsewhere;[15–17,20] however, they are briefly discussed below in conjunction with relevant details about the surveillance cohort.

Study site selection

A complete list of all health facilities in the City-Province of Kinshasa, DRC was obtained from the Ministry of Health. From this list, ten health facilities were randomly selected from a subset list of health facilities that 1) were designated as delivery centers, 2) recorded at least 1,000 annual deliveries in 2018, and 3) archived their birth records on site: Bomoi, Bondeko, Lisanga, Siloe Bdom, and Bosembo Health Centers; Esengo, Mokali, Saint Joseph, and Kinshasa General Reference Hospitals; and Ngaliema Clinic (Figure 2.1). These ten health facilities served as the study sites for both the retrospective and prospective cohorts. For the surveillance cohort, no study sites were explicitly identified; furthermore, no health facilities were excluded from the surveillance cohort in order to create a sample representative of the general population in Kinshasa.

Study procedures

For the retrospective cohort, archival medical records of mother-child pairs from births taking place in the study site health facilities between July 1, 2019 and August 31, 2020 were collected and digitized. For birth records that indicated the occurrence of an adverse birth outcome, additional module completion required for verification, which required seeking subject medical history beyond the birth record, was performed. A third module detailing maternal variables was also completed, usually requiring information from the mothers' archived antenatal care (ANC) records, when available. For all identified births, only medical information that could be found within the child's birth record or that could be linked to the child's birth record from another record within the same study site was utilized; additionally, only medical records with valid date of birth (DOB) information were included to ensure that only births that occurred between July 1, 2019 and August 31, 2020 were in the final sample.

For the prospective cohort, study participants were actively recruited and enrolled via convenience sampling upon visiting a study site health facility for an ANC visit or delivery from September 1, 2020 through January 31, 2021. Any pregnant woman 18 years of age or older who attended a study site health facility during the study period was eligible for inclusion. The study team recruited potential participants while 1) expectant mothers were visiting selected delivery facilities for regular ANC at 32 weeks or beyond in their pregnancy, or 2) following a postpartum mother's delivery once all medical necessities had been met, but while the mother remained for recovery and observation prior to discharge. After their delivery, enrolled mothers were administered an electronic surveillance questionnaire that captured demographic and clinical information and collected postpartum details related to the pregnancy and delivery, such as newborn DOB (which was a requirement for inclusion in order to be consistent with the retrospective cohort); medical records were also consulted as necessary in order to collect additional information.

For the surveillance cohort, no active data collection took place; rather, the previously established DHIS2 database was used to create the surveillance cohort (via aggregated dataset download from the DHIS2 server in August 2022). The DHIS2 is the world's largest health information management platform and is used in over one hundred countries.[21] In the DRC specifically, the Ministry of Health started to adopt the DHIS2 as the national health information system beginning in 2014.[22] Since its implementation, there has been a rapid rollout of the software and associated training programs throughout the country; as a result, an average of 92% of participating health facilities submitted reports of some kind to the national DHIS2 database each month in 2017.[23] For our purposes here, the surveillance cohort was created by filtering the national DRC DHIS2 database to only include patients who delivered at healthcare facilities in Kinshasa across the same time period as the retrospective and prospective cohorts (i.e., from July 1, 2019 to January 31, 2021).

Outcome measures

As there was incomplete overlap between the data elements captured in the archival medical records/enhanced monitoring data and the DHIS2 data, only the following four outcome measures were examined here: 1) mothers under 20 years of age, 2) stillbirth, 3) LBW, and 4) PTB. For most of the outcomes, the definitions used in the retrospective and prospective cohorts were virtually identical to the definitions used in the surveillance cohort; for example, LBW was defined according to the WHO cutoff (i.e., a birth weight less than 2,500 grams)[24] across all cohorts. For PTB though, there was a slight discrepancy; more specifically, instances of PTB screened positive by meeting either one of two criteria in the retrospective and prospective cohorts: PTB designation or presence of a gestational age at birth recorded as less than 37 weeks (based on last menstrual period [LMP] and/or ultrasound information) in the medical record/surveillance questionnaire. The DHIS2 dataset, on the other hand, simply recorded occurrence of "premature births" (Supplemental Table 2.1). In addition to these outcome measures, other relevant variables (e.g., deliveries attended by skilled birth attendant, general reference hospital deliveries, etc.) were also examined due to their potential confounding effect.

Statistical analysis

The crude prevalence of each variable was estimated with a corresponding 95% confidence interval (CI), assuming a binomial distribution, within each of the three cohorts; the amount of missingness for each variable was also assessed for the retrospective and prospective cohorts. Two types of outcome measure comparisons were made: 1) a comparison of the prevalence estimates between the retrospective and surveillance cohorts during their overlapping periods and 2) a comparison of the prevalence estimates between the prospective and surveillance cohorts during their overlapping time periods. Thus, comparisons were not made directly between the retrospective and prospective cohorts. For each pair of prevalence estimates across the four outcomes, the percentage-point difference in outcome measure prevalence estimates was produced along with corresponding 95% CIs. Moreover, graphical representations of the prevalence estimates using monthly time series were generated to visually describe the prevalence trends and identify any outlier months. Because individual level data were not available for the surveillance cohort, adjusted prevalence estimates and associated comparisons were computed by applying the distribution of the confounding variable(s) from the surveillance cohort to the retrospective and prospective cohorts (i.e., by a simple weighting procedure) in order to remove their confounding effect. Additionally, such measures were further adjusted by accounting for clustering at the health-facility level within the retrospective and prospective cohorts.

For all outcome measure prevalence comparisons, the two one-sided test (TOST) for equivalence was used to determine whether the compared prevalence estimates were statistically equivalent. In the TOST procedure, two null hypotheses are generated: $H_1: p_1 - p_2 \leq -\delta$ and $H_2: p_1 - p_2 \geq \delta$, where $p_1$refers to the prevalence in cohort one, $p_2$refers to the prevalence in cohort two, and δ refers to the pre-specified equivalence margin; the first null hypothesis is rejected when $z_1 \geq z_{1-\alpha}$, and the second null hypothesis is rejected when $z_2 \leq z_{\alpha}$. When both null hypotheses are rejected, we can reject the overall null hypothesis that the difference in the proportions is greater than δ (i.e., $-\delta < p_1 - p_2 < \delta$); thus, we would conclude that the difference in the proportion falls within the equivalence margin.[25,26] For our purposes, we used both a ± five percentage point equivalence margin (i.e., the traditional margin) as well as a ± two and a half percentage point equivalence margin, as research by Tatem et al. suggests that this margin is the "most appropriate" for health indicators with a prevalence of less than ten percent.[27] Regardless of equivalence margin, 90% CIs – which correspond to an $\alpha = 0.05$ in the context of the TOST procedure[28,29] – were produced for all TOST equivalence comparisons.

Lastly, potential outliers were assessed according to Cook's distance, and their influence was determined by seeing how the results changed after their removal. All statistical analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria); additionally, TOST equivalence comparisons were computed using the *TOSTER* package.[30,31]

Informed consent and ethical approval

For the retrospective and surveillance cohorts, no informed consent process took place as no active participant recruitment or enrollment were performed. For the prospective cohort, oral informed consent took place at the time of enrollment in either French or Lingala since many participants were illiterate; participants were informed about the purpose of the study, the data that would be collected, and the potential risks and benefits of participation. Importantly, it was made clear to the participants that the decision of whether or not to participate in the study would not affect the care they received at study site delivery centers. Lastly, a copy of the consent form was provided to each participant. Institutional review board (IRB) approval was obtained from the University of California, Los Angeles (IRB#19-002150) as well as the Kinshasa School of Public Health at the University of Kinshasa (ESP/CE/300/2019), which served as the local ethics committee, to perform the retrospective and prospective cohort data collection/analysis procedures. Because the surveillance cohort comprised of de-identified secondary data, its use/analysis met the criteria for exemption from IRB review.

2.4. Results

Crude prevalence estimates

For the retrospective cohort, 14,300 medical records were initially abstracted; however, 44 medical records were excluded because they had missing and/or incorrect DOB information resulting in a final sample size of 14,256 deliveries. For the prospective cohort, 2,675 women were initially enrolled; however, after accounting for non-singleton deliveries (5.98%) and the exclusion of deliveries with missing/incorrect DOB information (*n* = 363), the final sample size was 2,472 deliveries. For the surveillance cohort, 305,953 deliveries were included in the final sample: 216,788 deliveries from July 1, 2019 through August 31, 2020 and 89,165 deliveries from September 1, 2020 through January 31, 2021. Crude prevalence estimates ranged from 3.51% (95% CI: 3.21%, 3.82%) for stillbirth to 12.67% (95% CI: 12.12%, 13.21%) for LBW in the retrospective cohort; similarly, crude prevalence estimates ranged from 2.79% (95% CI: 2.14%, 3.44%) for stillbirth to 10.39% (95% CI: 9.19%, 11.60%) for LBW in the prospective cohort. In the surveillance cohort, crude prevalence estimates for stillbirth, LBW, and PTB were lower compared to the retrospective and prospective cohorts; however, the crude prevalence estimates for mothers under 20 years of age were higher in the surveillance cohort compared to the retrospective and prospective cohorts (Table 2.1).

In both the retrospective and prospective cohorts, stillbirth, LBW, and PTB were nearly completely observed (i.e., missingness was less than 5% across outcomes); however, missingness for mothers under 20 years of age was between 10% and 15% in both the retrospective and prospective cohorts. Missingness information for the surveillance cohort was not able to be directly assessed because the associated data outputs were downloaded in aggregated form. Regarding potential confounding variables, it was found that only 1.99% of the recorded deliveries were referred to a general reference hospital in the surveillance cohort; however, 9.33% and 8.65% of recorded deliveries were performed at a general reference hospital (i.e., Kinshasa General Reference Hospital) in the retrospective and prospective cohorts, respectively, thereby indicating potential confounding as general reference hospitals generally see more high-risk pregnancies compared to non-general reference hospitals. Prevalence estimates for other variables assessed (such as deliveries attended by a skilled birth attendant) were virtually the same across the three cohorts and thus not considered confounders (data not shown).

Adjusted prevalence estimates and comparisons

After adjusting the crude results by weighting the retrospective and prospective cohorts according to the distribution of the general reference hospitals in the surveillance cohort, the prevalence estimates for stillbirth, LBW, and PTB decreased slightly while the mothers under 20 years of age prevalence estimate remained about the same. Adjusted prevalence comparisons revealed that the difference between the retrospective and surveillance cohorts was -5.65% (95% CI: -6.09%, -5.20%) for mothers under 20 years of age, 0.31% (95% CI: 0.06%, 0.56%) for stillbirth, 1.98% (95% CI: 1.45%, 2.51%) for LBW, and 5.92% (95% CI: 5.47%, 6.38%) for PTB. Similarly, adjusted prevalence comparisons showed that the difference between the prospective and surveillance cohorts was -7.93% (95% CI: -8.70%, -7.17%) for mothers under 20 years of age, 0.20% (95% CI: -0.35%, 0.74%) for stillbirth, 1.36% (95% CI: 0.24%, 2.49%) for LBW, and 3.61% (95% CI: 2.72%, 4.51%) for PTB (Table 2.2).

Adjusted monthly time series demonstrated that there was near-complete overlap in the monthly prevalence estimates for stillbirth between both the retrospective and prospective cohorts and the surveillance cohort. For LBW, there was substantial overlap in the monthly prevalence estimates between the prospective and surveillance cohorts; however, there was slightly less overlap for LBW between the retrospective and surveillance cohorts. For mothers under 20 years of age and PTB though, there was no overlap in the monthly prevalence estimates between both the retrospective and prospective cohorts and the surveillance cohort (Figure 2.2).

Equivalence analysis

When assessing the percentage point differences between the retrospective and surveillance cohorts, it was found that the mothers under 20 years of age (90% CI: -6.04%, -5.33%) and PTB (90% CI: 5.51%, 6.29%) estimates were not statistically equivalent regardless of which equivalence margin was used. However, the stillbirth (90% CI: 0.11%, 0.48%) and LBW (90% CI: 1.53%, 2.41%) estimates were found to be statistically equivalent using both a ± five percentage point and a ± two and a half percentage point equivalence margin. When assessing the percentage point differences between the prospective and surveillance cohorts, results were mostly similar. For example, the stillbirth (90% CI: -0.30%, 0.69%) and LBW (90% CI: 0.41%, 2.28%) estimates were found to be statistically equivalent using either equivalence margin, while the mothers under 20 years of age estimates (90% CI: -8.64%, -7.31%) were not statistically equivalent regardless of equivalence margin. However, the PTB estimates (90% CI: 2.85%, 4.38%) were statistically equivalent using a ± five percentage point equivalence margin only (Figure 2.3).

Results were mostly consistent when accounting for clustering at the health-facility level within the retrospective and prospective cohorts. For instance, the mothers under 20 years of age estimates were still not statistically equivalent regardless of equivalence margin for both comparison types; similarly, the stillbirth estimates were still statistically equivalent using either equivalence margin for both comparison types. However, the LBW estimates were now statistically equivalent using a ± five percentage point equivalence margin only for both comparison types. Additionally, PTB estimates were now not statistically equivalent regardless of which equivalence margin was used for both comparison types (Figure 2.4).

Outlier assessment

Within the adjusted monthly time series (Figure 2.2), the November 2019 prevalence estimate for the mothers under 20 years of age variable within the surveillance cohort was identified as a possible outlier that may have influenced the corresponding prevalence comparison between the retrospective and surveillance cohorts. Outlier analysis via Cook's distance confirmed that the November 2019 prevalence estimate was in fact an outlier (Supplemental Figure 2.1). As a result, the surveillance cohort prevalence estimate from July 1, 2019 through August 31, 2020 was recalculated excluding the November 2019 observation; however, it was found that the prevalence estimate did not change substantially (i.e., from 12.84% to 12.36%), and thus associated equivalence analyses were not performed.

2.5. Discussion

Summary

This study compared prevalence estimates of four key health measures (i.e., mothers under 20 years of age, stillbirth, LBW, and PTB) from both (retrospective) archival medical records and (prospective) enhanced monitoring data to surveillance data in the form of the DHIS2. Through this investigation, we determined that the adjusted prevalence estimates of two health measures – stillbirth and LBW – were statistically equivalent between both the retrospective and prospective cohorts and the surveillance cohort; however, we also found that the adjusted prevalence estimates of the other two health measures – mothers under 20 years of age and PTB – were generally not statistically equivalent between both the retrospective and prospective cohorts and the surveillance cohort. Nonetheless, our results still suggest that archival medical records and enhanced monitoring data can be validly used as alternative – and perhaps superior – PV tools for the surveillance of maternal and neonatal health outcomes in Kinshasa, DRC.

Literature comparisons for stillbirth, LBW, and PTB

Indeed, not only were the adjusted prevalence estimates generated from the archival medical records and the enhanced monitoring data for stillbirth and LBW statistically equivalent to the corresponding DHIS2 prevalence estimates, but they were also generally in line with the literature in this area. For instance, a systematic assessment of the global burden of stillbirth determined that the national stillbirth prevalence in the DRC was 2.72% (90% uncertainty interval: 2.17%, 3.43%) in 2019.[32] Within Kinshasa, stillbirth prevalence studies were not identified; however, other studies conducted in more rural parts of the country reported stillbirth prevalences ranging from 3.00% to 3.89%.[33–37] Similar literature supports our LBW findings from the archival medical records/enhanced monitoring data. For example, a systematic analysis of global LBW trends found that the national LBW prevalence in the DRC was 10.80% (95% CI: 10.70%, 10.90%) in 2015.[38] As was the case with stillbirth, LBW prevalence studies were not identified in Kinshasa. Nevertheless, a 2021 cross-sectional study within urban and rural hospitals in Kasaï-Central province reported a LBW prevalence of 11.30%;[39] relatedly, a retrospective analysis among postpartum women and their newborns in semi-rural Kamina from 2009 to 2010 reported a LBW prevalence of 14.30%.[40] It should be noted that though the stillbirth and LBW prevalence estimates from the archival medical records and enhanced monitoring data were in fact lower than the estimates from the aforementioned rural studies,[33–37,39,40] this finding is expected as Kinshasa is one of the wealthiest and most urbanized provinces within the DRC.[41]

Regarding PTB, the prevalence estimates generated from the archival medical records and enhanced monitoring data were higher than the estimates generated from the DHIS2 surveillance dataset. Though this finding could be interpreted as a limitation of the archival medical records and enhanced monitoring data for future PV purposes, comparisons with the literature suggest that these alternative data sources may in fact better record PTB prevalence than the DHIS2. For example, a systematic review and modelling analysis of the global burden of PTB determined that the national PTB prevalence in the DRC was 9.83% (96% uncertainty interval: 7.08%, 13.16%) in 2014,[42] a prevalence much more in line with estimates generated from the archival medical records/enhanced monitoring data compared to the DHIS2 data. While no prevalence studies were identified in Kinshasa, the previously mentioned retrospective analysis among postpartum women and their newborns in semi-rural Kamina reported a PTB prevalence of 17.10%;[39] a 2006 study in the rural province of Maniema also reported an increased prevalence of PTB (i.e., 21.91%).[43] Although these PTB prevalence estimates are higher than the adjusted estimates found from the archival medical records/enhanced monitoring data (i.e., 5.40% to 8.33%), they are still closer than the surveillance estimates produced from the DHIS2 dataset (i.e., 1.78% to 2.41%). Likewise, other research has suggested that the DHIS2 underestimates PTB in the DRC.[44] Additionally, the surveillance cohort PTB prevalence estimates are even lower than associated estimates commonly found for HICs,[42,45] thereby further indicating that the DRC DHIS2 dataset may in fact be underestimating PTB.

Additional considerations for PTB and mothers under 20 years of age

A key reason for the discrepancy in PTB estimates between the cohorts may be the fact that we did not only screen for the presence of PTB in the retrospective and prospective cohort studies, but we also factored in gestational age information to identify additional cases of PTB that may not have been categorized as such in the archival medical records and/or active surveillance questionnaires. In general, PTB is a difficult outcome to measure because it "is defined by time, not by a distinctive clinical phenotype."[46] Consequently, accurate dating of the LMP as well as access to clinical and ultrasonographic evaluations are necessary for valid measurement; however, the availability of such information can vary widely across health facilities.[47] In LMICs, assessing the burden of PTB is especially challenging due to limited use of ultrasound biometry; thus, healthcare workers in LMICs typically rely on LMP, which can underestimate gestational age, to asses PTB status.[48–50] Thus, our detailed approach that incorporated the use of gestational age information from LMP and ultrasounds measurements (where available) to enrich the number of identified PTB cases may have helped overcome some of the challenges traditionally associated with the surveillance of PTB in low-resource settings.

Nonetheless, it must be acknowledged that there were wide discrepancies in the prevalence estimates for the mothers under 20 years of age variable across cohorts (even after the removal of an outlier observation). As opposed to PTB where the discrepancies favored the archival medical records/enhanced monitoring data, the opposite was true for the mothers under 20 years of age variable in that the literature generally agreed with the DHIS2 estimate; for instance, a 2021 Guttmacher Institute report stated that women under 20 years of age in Kinshasa represented about 13.0% of the city's total pregnancies in 2016.[51,52] A likely explanation for this divergence between the retrospective/prospective cohorts and the surveillance cohort is that moderate missingness was observed for maternal age in both the archival medical records and the enhanced surveillance data, thereby leading to a potentially inaccurate measure of mothers under 20 years of age in those data sources. Additionally, the prospective cohort excluded mothers below the age of 18 and used convenience sampling to enroll participants. Therefore, the nature of the entry criteria and data collection likely contributed to an overall older sample than would be expected for the Kinshasa general population; these factors may help explain why the adjusted difference between the prospective and surveillance cohorts (i.e., -7.93%) was in fact larger in absolute terms than the adjusted difference between the retrospective and surveillance cohorts (i.e., -5.65%) for the mothers under 20 years of age variable.

PV implications

Despite these issues associated with maternal age measurement, our results still suggest that archival medical records and enhanced monitoring data can be used as alternative and/or supplementary tools for PV activities in Kinshasa. Although the DHIS2 dataset can be an appropriate tool for the monitoring of certain health outcomes in the DRC, it is limited in its scope; for example, the Congolese DHIS2 system does not record information on the prevalence of neonatal seizures. Furthermore, the aggregated nature of the DHIS2 data does not allow for individually linking a woman's maternal immunization history with her child's health outcomes, thereby making it an inadequate tool for AEFI surveillance at a population level. Moreover, other researchers have documented data quality/missing data issues associated with the DHIS2 and other routine health information systems from LMICs.[53,54] Consequently, other data sources should be employed in the DRC to increase PV capabilities and adequately monitor the full range of neonatal health outcomes.

By determining that archival medical records and enhanced monitoring data may accurately measure the prevalence of adverse birth outcomes, this study represents a key step in potentially expanding the means for the surveillance of maternal and neonatal health outcomes in Kinshasa. This analysis thus has implications for the Congolese PV infrastructure and provides evidence in favor of utilizing archival medical records/enhanced monitoring data (in conjunction with spontaneous reporting mechanisms and DHIS2 surveillance) to address vaccine/drug safety inquiries more effectively in Kinshasa. However, in order to be more valuable PV tools, future work should be geared towards more accurately capturing maternal age information (especially in the archival medical records); likewise, PV investigations aimed at general population estimates should be sure to not impose exclusion criteria based on maternal age. Nonetheless, we hope these results will spur more widespread use of archival medical records and/or enhanced monitoring data, thereby supporting Nzolo et al.'s call for the increased application of health information systems and other innovative data sources to supplement current PV programs in the DRC.[8]

Strengths and limitations

In support of our findings, the major strength of this study was the use of the TOST procedure over standard hypothesis testing methods (i.e., difference testing). A limitation of the classical difference testing approach is that the absence of an effect (i.e., a difference between prevalence estimates) can be rejected but not statistically supported; thus, one can only conclude that the lack of a difference is consistent with no effect, assuming that the null hypothesis is true. The TOST procedure, on the other hand, allows for the establishment of equivalence due to the fact that the null hypothesis is that the two prevalence estimates differ by more than a pre-specified amount.[27,30] Another advantage of the TOST procedure is that it is not as affected by large sample sizes; large sample sizes present a problem for classical difference testing procedures because such methods may lead to statistically significant results that are not actually meaningful.[27,30] Another strength of this investigation was that it built on previous work that focused on the diagnostic capability of archival medical records/enhanced monitoring data and found that such data sources could feasibly capture a variety of maternal and neonatal health outcomes via the Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) criteria;[15–17] this analysis thus further solidifies the justification for the utilization of archival medical records and enhanced monitoring data for PV and surveillance purposes in the DRC.

Nevertheless, there are several limitations of this investigation that must also be considered. For example, differences in data collection methods/variable definitions across the cohorts may have introduced some levels of information bias, thereby potentially impacting the validity of our interpretations. Relatedly, all three cohorts had data elements that were incompletely observed and/or inconsistently reported (thereby potentially leading to information and selection biases). However, missing data are common features of real-world data sources used for PV and surveillance purposes,[5–7,53,54] so this limitation is not unique to the analysis done here; still, future investigations in this area should aim to employ multiple imputation methods (as feasible) to overcome this limitation. Furthermore, due to low levels of variable overlap between the DHIS2 data and the archival medical records/enhanced monitoring data, we were only able to account for the effect of one confounding variable (i.e., deliveries performed at general reference hospitals) in our analyses; consequently, other variables (such as socioeconomic status, number of ANC visits, previous medical history, etc.) were not factored into the analyses, thereby likely leading to some uncontrolled confounding.

Moreover, the results of this study may not be generalizable outside of Kinshasa; therefore, our conclusions made about the suitability of the archival medical records/enhanced monitoring data may not necessarily apply to other large urban areas in the DRC. Somewhat relatedly, our analysis only included deliveries that occurred in larger health facilities with on-site storage of birth records; as a result, home births and deliveries that occurred in smaller/less developed health facilities were excluded, potentially leading to the introduction of selection bias (assuming that home births/other institutional deliveries had a differential risk of adverse birth outcomes occurrence). Additionally, it should be noted that the COVID-19 pandemic officially reached the DRC about halfway through this study (i.e., on March 10, 2022);[55] thus, it is possible that the impact of the COVID-19 pandemic along with the associated governmental response may have affected certain cohorts more than others, thereby potentially undermining the validity of the comparisons conducted here. Lastly, we did not directly compare the retrospective to the prospective cohort due to differences in data collection methods and time periods; however, our results indicated that the prevalence estimates for our outcomes were consistently lower in the prospective cohort compared to the retrospective cohort. Future investigations should therefore aim to directly compare archival medical records and enhanced monitoring data and evaluate the reasons behind potential discrepancies (if any) so that their utility as PV tools can be better understood.

Conclusion

Notwithstanding these limitations, this study succeeded in comparing selected prevalence estimates from both archival medical records and enhanced monitoring data to those from the DHIS2 in order to assesses the suitability of the archival medical records/enhanced monitoring data for PV purposes in Kinshasa, DRC. Our results suggested that these alternative data sources are indeed suitable tools for the monitoring of adverse birth outcomes in Kinshasa, though issues were identified in their ability to accurately measure maternal age. Nonetheless, we hope that our findings lead to more widespread use and increased acceptance of alternative data in the form of archival medical records and enhanced monitoring data in order to bolster the ability of researchers to better monitor maternal and neonatal health – including the safety of associated pharmaceutical interventions – in the DRC.

2.6. Tables and Figures

Table 2.1. Crude cohort prevalence percentage estimates among deliveries in Kinshasa, DRC from July 1, 2019 through January 31, 2021

Outcome Measure	July 1, 2019 through August 31, 2020		September 1, 2020 through January 31, 2021	
	Retrospective Prevalence (95% CI) *N = 14,256*	Surveillance Prevalence (95% CI) *N = 216,788*	Prospective Prevalence (95% CI) *N = 2,472*	Surveillance Prevalence (95% CI) *N = 89,165*
Mothers under 20 years of age	7.29% (6.86%, 7.71%)	12.84% (12.70%, 12.98%)	3.68% (2.94%, 4.42%)	11.57% (11.36%, 11.78%)
Stillbirth	3.51% (3.21%, 3.82%)	1.93% (1.88%, 1.99%)	2.79% (2.14%, 3.44%)	1.73% (1.64%, 1.81%)
LBW	12.67% (12.12%, 13.21%)	9.12% (9.00%, 9.24%)	10.39% (9.19%, 11.60%)	7.26% (7.09%, 7.43%)
PTB	10.15% (9.65%, 10.65%)	2.41% (2.34%, 2.47%)	7.00% (5.99%, 8.00%)	1.78% (1.70%, 1.87%)

CI = confidence interval, DRC = Democratic Republic of the Congo, LBW = low birth weight, PTB = preterm birth.

Table 2.2. Adjusted cohort prevalence percentage estimates and comparisons among deliveries in Kinshasa, DRC from July 1, 2019 through January 31, 2021

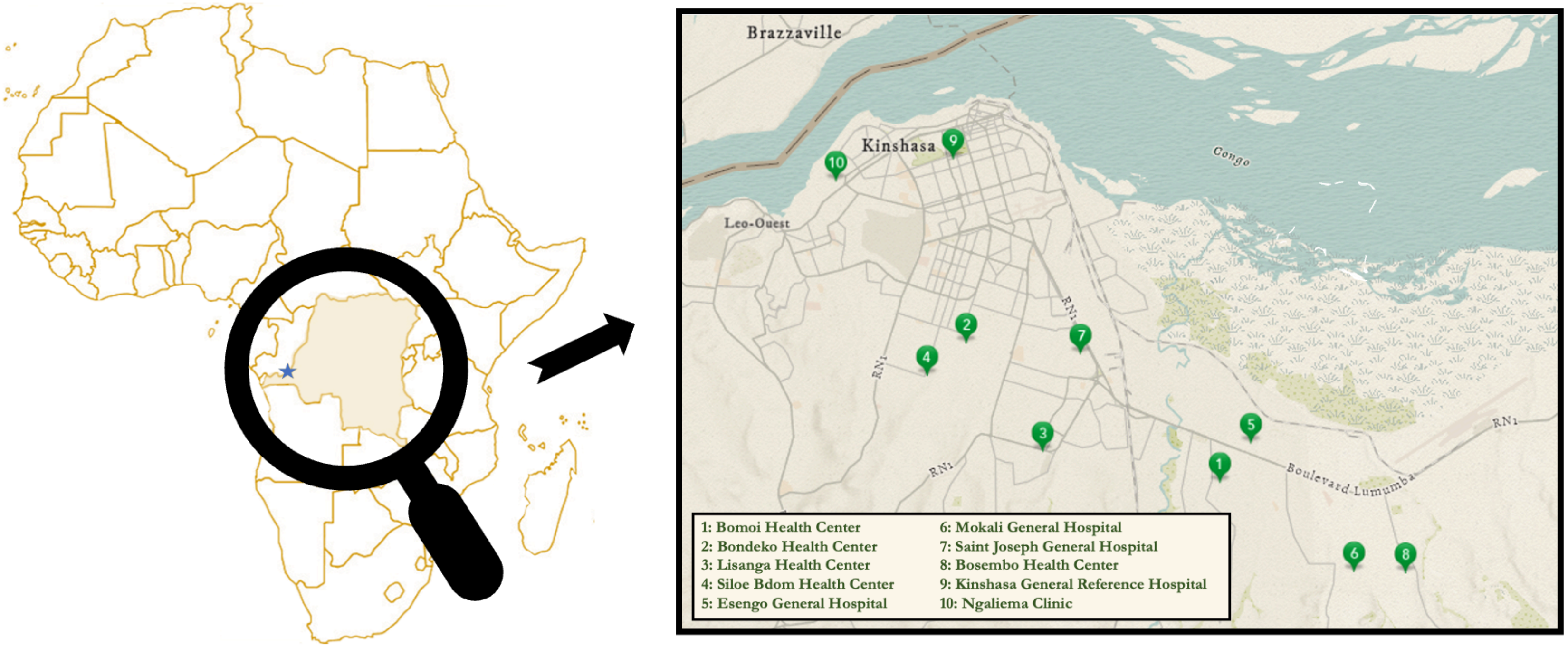
Outcome Measure	Retrospective vs. Surveillance Cohort Comparisons (July 1, 2019 through August 31, 2020)			Prospective vs. Surveillance Cohort Comparisons (September 1, 2020 through January 31, 2021)		
	Retrospective Prevalence (95% CI) *N = 14,256*	Surveillance Prevalence (95% CI) *N = 216,788*	Prevalence Difference† (95% CI)	Prospective Prevalence (95% CI) *N = 2,472*	Surveillance Prevalence (95% CI) *N = 89,165*	Prevalence Difference† (95% CI)
Mothers under 20 years of age	7.19% (6.77%, 7.62%)	12.84% (12.70%, 12.98%)	-5.65% (-6.09%, -5.20%)	3.63% (2.90%, 4.37%)	11.57% (11.36%, 11.78%)	-7.93% (-8.70%, -7.17%)
Stillbirth	2.24% (2.00%, 2.49%)	1.93% (1.88%, 1.99%)	0.31% (0.06%, 0.56%)	1.92% (1.38%, 2.47%)	1.73% (1.64%, 1.81%)	0.20% (-0.35%, 0.74%)
LBW	11.10% (10.58%, 11.61%)	9.12% (9.00%, 9.24%)	1.98% (1.45%, 2.51%)	8.63% (7.52%, 9.74%)	7.26% (7.09%, 7.43%)	1.36% (0.24%, 2.49%)
PTB	8.33% (7.87%, 8.79%)	2.41% (2.34%, 2.47%)	5.92% (5.47%, 6.38%)	5.40% (4.50%, 6.30%)	1.78% (1.70%, 1.87%)	3.61% (2.72%, 4.51%)

CI = confidence interval, DRC = Democratic Republic of the Congo, LBW = low birth weight, PTB = preterm birth.

†Prevalence Difference = Retrospective/Prospective Cohort Prevalence – Surveillance Cohort Prevalence.

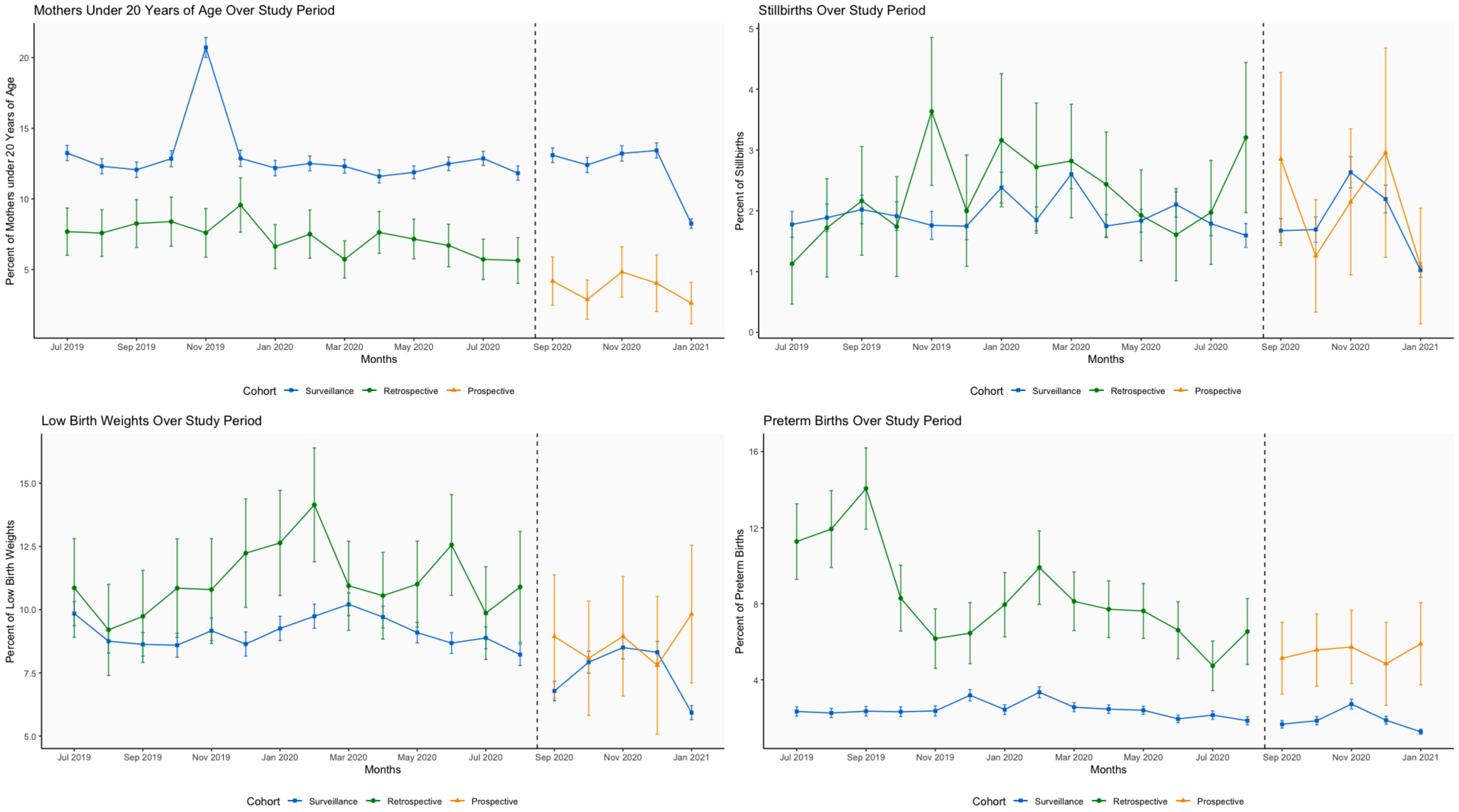
Adjusted cohort prevalence estimates and comparisons computed by weighting the crude results from the retrospective and prospective cohorts according to the distribution of the general reference hospitals from the surveillance cohort.

Figure 2.1. Location of study site health facilities in the retrospective and prospective cohorts, Kinshasa, DRC



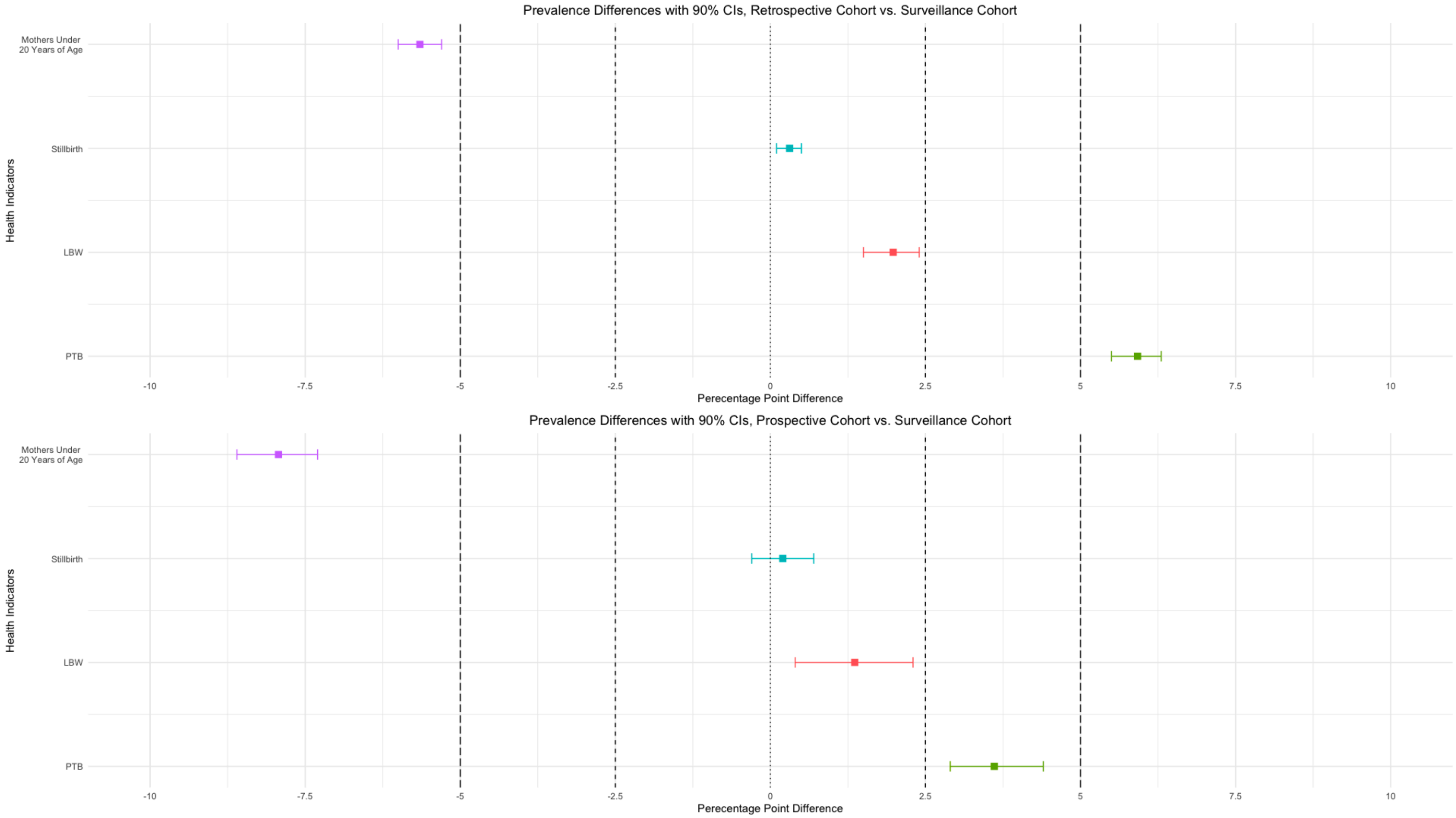
DRC = Democratic Republic of the Congo.

Figure 2.2. Adjusted monthly prevalence estimates for each outcome measure over the study period, by cohort



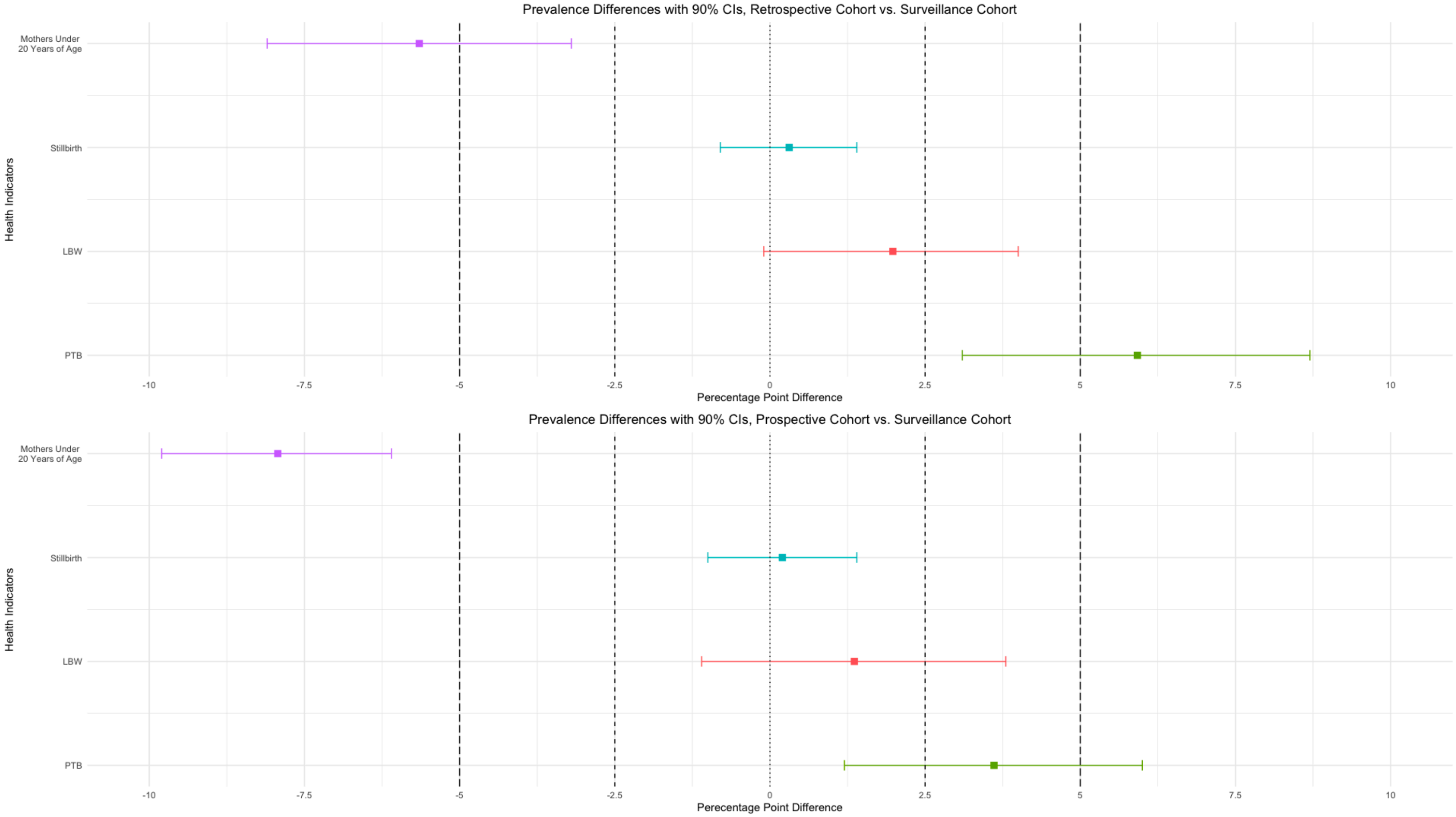
Adjusted prevalence estimates computed by weighting the crude results from the retrospective and prospective cohorts according to the distribution of the general reference hospitals from the surveillance cohort.

Figure 2.3. Adjusted prevalence comparisons with two TOST equivalence margins, by comparison set



TOST = two one-sided test. Adjusted prevalence estimates computed by weighting the crude results from the retrospective and prospective cohorts according to the distribution of the general reference hospitals from the surveillance cohort.

Figure 2.4. Adjusted prevalence comparisons with two TOST equivalence margins, by comparison set, accounting for clustering at the health-facility level



TOST = two one-sided test. Adjusted prevalence estimates computed by weighting the crude results from the retrospective and prospective cohorts according to the distribution of the general reference hospitals from the surveillance cohort.

2.7. Appendix

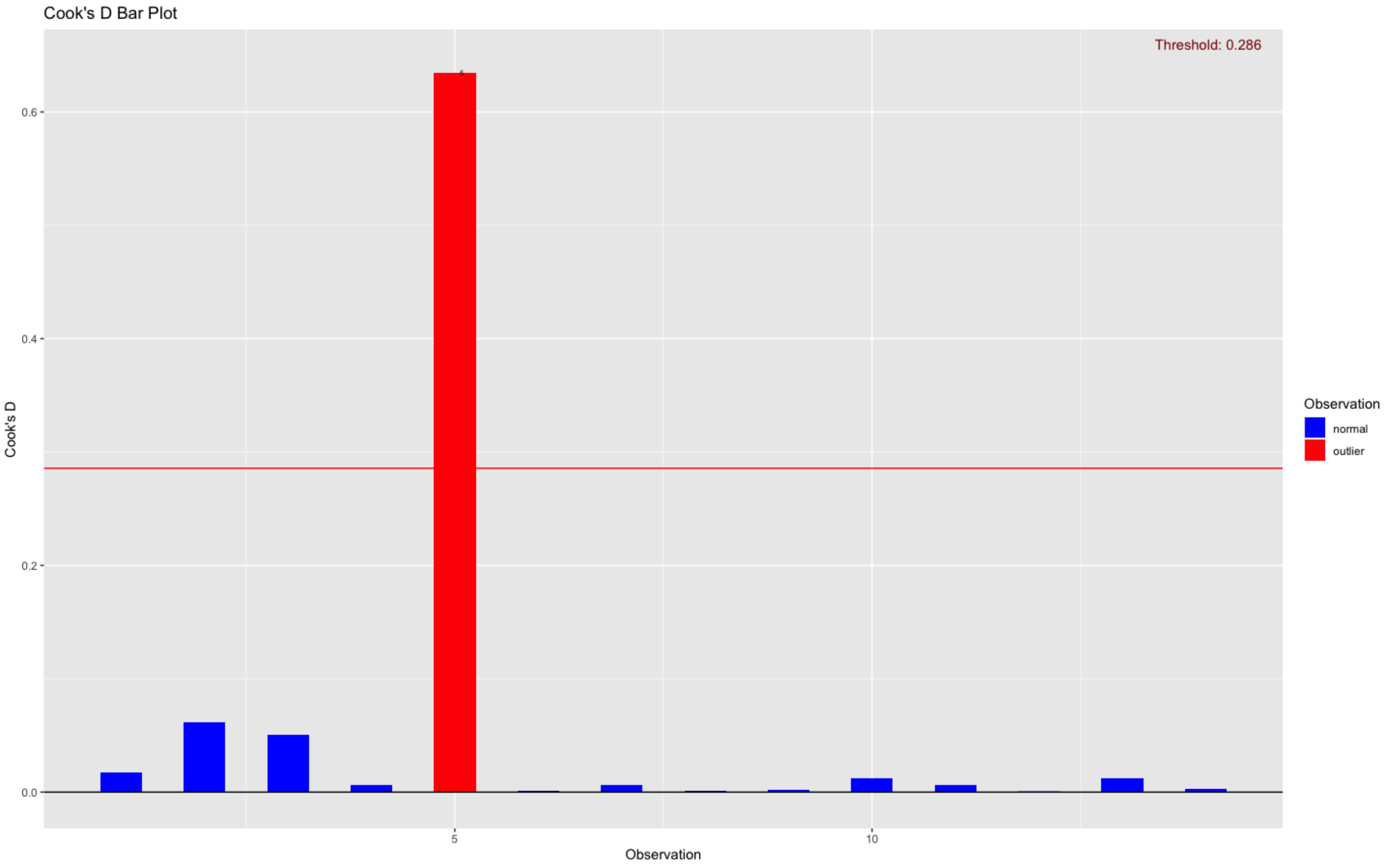
Supplemental Table 2.1. Outcome variables and their associated definitions

Outcome Variable	**Retrospective Cohort Definition**	**Prospective Cohort Definition**	**Surveillance Cohort Definition**	
			Verbatim (French)	**Translation (English)**
Mothers under 20 years of age	Maternal age at delivery (years)	Maternal age at delivery (years)	Accouchée âgée de moin de 20 ans	Childbirth under 20 years of age
Stillbirth	Any instance of stillbirth* (either intra- or post-partum)	Any instance of stillbirth* (either intra- or post-partum)	Mort-nés frais/Mort-nés macérés	Fresh stillbirth/ macerated stillbirth
LBW	Newborn weight less than 2,500 grams	Newborn weight less than 2,500 grams	Nouveaux-nés avec moins de 2500 grammes	Newborns with less than 2,500 grams
PTB	PTB designation or presence of a gestational age at birth less than 37 weeks	PTB designation or presence of a gestational age at birth less than 37 weeks	Nouveaux nés prématurés	Premature birth

LBW = low birth weight, PTB = preterm birth.

*Defined per standard practice (i.e., the birth of a baby following fetal death either before [antepartum stillbirth] or during labor/birth [intrapartum stillbirth]).[32]

Supplemental Figure 2.1. Results of outlier analysis using Cook's distance



2.8. References

1. World Health Organization. Pharmacovigilance. Accessed October 28, 2021. https://www.who.int/teams/health-product-and-policy-standards/about/regulation-and-prequalification

2. Beninger P. Pharmacovigilance: An Overview. *Clin Ther*. 2018;40(12):1991-2004. doi:10.1016/j.clinthera.2018.07.012

3. Fornasier G, Francescon S, Leone R, Baldo P. An historical overview over Pharmacovigilance. *Int J Clin Pharm*. 2018;40(4):744-747. doi:10.1007/s11096-018-0657-1

4. Liu F, Jagannatha A, Yu H. Towards Drug Safety Surveillance and Pharmacovigilance: Current Progress in Detecting Medication and Adverse Drug Events from Electronic Health Records. *Drug Saf*. 2019;42(1):95-97. doi:10.1007/s40264-018-0766-8

5. Nissen F, Quint JK, Morales DR, Douglas IJ. How to validate a diagnosis recorded in electronic health records. *Breathe Sheff Engl*. 2019;15(1):64-68. doi:10.1183/20734735.0344-2018

6. Russell LB. Electronic Health Records: The Signal and the Noise. *Med Decis Making*. 2021;41(2):103-106. doi:10.1177/0272989X20985764

7. Beaulieu-Jones BK, Lavage DR, Snyder JW, Moore JH, Pendergrass SA, Bauer CR. Characterizing and Managing Missing Structured Data in Electronic Health Records: Data Analysis. *JMIR Med Inform*. 2018;6(1):e8960. doi:10.2196/medinform.8960

8. Nzolo D, Kuemmerle A, Lula Y, et al. Development of a pharmacovigilance system in a resource-limited country: the experience of the Democratic Republic of Congo. *Ther Adv Drug Saf*. 2019;10:2042098619864853. doi:10.1177/2042098619864853

9. Nzolo D, Ntetani Aloni M, Mpiempie Ngamasata T, et al. Adverse events following immunization with oral poliovirus in Kinshasa, Democratic Republic of Congo: preliminary results. *Pathog Glob Health*. 2013;107(7):381-384. doi:10.1179/2047773213Y.0000000113

10. Nzolo D, Engo Biongo A, Kuemmerle A, et al. Safety profile of fractional dosing of the 17DD Yellow Fever Vaccine among males and females: Experience of a community-based pharmacovigilance in Kinshasa, DR Congo. *Vaccine*. 2018;36(41):6170-6182. doi:10.1016/j.vaccine.2018.08.052

11. Ntamabyaliro NY, Burri C, Nzolo DB, et al. Drug use in the management of uncomplicated malaria in public health facilities in the Democratic Republic of the Congo. *Malar J*. 2018;17:189. doi:10.1186/s12936-018-2332-3

12. Nzolo D, Anto F, Hailemariam S, et al. Central and Peripheral Nervous System Disorders Following Ivermectin Mass Administration: A Descriptive Study Based on the Democratic Republic of Congo Pharmacovigilance System. *Drugs - Real World Outcomes*. 2017;4(3):151-158. doi:10.1007/s40801-017-0110-0

13. Zielinski C, Kebede D, Mbondji PE, Sanou I, Kouvividila W, Lusamba-Dikassa PS. Knowledge systems in health in sub-Saharan Africa: results of a questionnaire-based survey. *J R Soc Med*. 2014;107(1_suppl):22-27. doi:10.1177/0141076813518525

14. Verbeke F, Shamashanga P, Amisi C, Karara G. Developing a national e-health strategy for DR Congo: a preliminary analysis of business needs, existing information systems and solutions. *J Health Inform Afr*. 2014;2(2). doi:10.12856/JHIA-2014-v2-i2-102

15. Gadoth A, Mukadi Nkamba D, Arena PJ, et al. Assessing the feasibility of passive surveillance for maternal immunization safety utilizing archival medical records in Kinshasa, Democratic Republic of the Congo. *Vaccine*. 2022;40(26):3605-3613. doi:10.1016/j.vaccine.2022.04.073

16. Arena PJ, Dzogang C, Gadoth A, et al. Comparison of adverse pregnancy and birth outcomes using archival medical records before and during the first wave of the COVID-19 pandemic in Kinshasa, Democratic Republic of Congo: a facility-based, retrospective cohort study. *BMC Pregnancy Childbirth*. 2023;23(1):31. doi:10.1186/s12884-022-05291-w

17. Arena PJ, Gadoth A, Nkamba DM, et al. Prospective assessment of pregnancy and birth outcomes using the Global Alignment of Immunization Safety Assessment in pregnancy criteria in Kinshasa, Democratic Republic of the Congo. *BMJ Public Health*. Under Review.

18. DHIS2. About DHIS2. DHIS2. Accessed October 28, 2021. https://dhis2.org/about/

19. Dehnavieh R, Haghdoost A, Khosravi A, et al. The District Health Information System (DHIS2): A literature review and meta-synthesis of its strengths and operational challenges based on the experiences of 11 countries. *Health Inf Manag J*. 2019;48(2):62-75. doi:10.1177/1833358318777713

20. Nkamba DM, Arena PJ, Gadoth A, et al. Adherence to face mask use during the COVID-19 pandemic among women seeking antenatal care in Kinshasa, Democratic Republic of Congo: a facility-based cross-sectional study. *BMJ Open*. 2022;12(7):e060929. doi:10.1136/bmjopen-2022-060929

21. DHIS2. In Action. DHIS2. Accessed November 12, 2021. https://dhis2.org/in-action/

22. MEASURE Evaluation. Mapping the Stages of MEASURE Evaluation’s Data Use Continuum to DHIS 2: An Example from the Democratic Republic of the Congo — MEASURE Evaluation. Published March 2019. Accessed October 28, 2021. https://www.measureevaluation.org/resources/publications/fs-19-344.html

23. IMA World Health. DHIS2. IMA World Health, DRC. Accessed November 12, 2021. https://imadrc.org/dhis2/

24. World Health Organization. Low birth weight. Accessed January 31, 2022. https://www.who.int/data/maternal-newborn-child-adolescent-ageing/advisory-groups/gama/gama-related-resources/nlis

25. Rogers JL, Howard KI, Vessey JT. Using significance tests to evaluate equivalence between two experimental groups. *Psychol Bull*. 1993;113(3):553-565. doi:10.1037/0033-2909.113.3.553

26. Shishkina T, Farmus L, Cribbie R. Testing for a lack of relationship among categorical variables. *Quant Methods Psychol*. Published online 2018. doi:10.20982/TQMP.14.3.P167

27. Tatem KS, Romo ML, McVeigh KH, et al. Comparing Prevalence Estimates From Population-Based Surveys to Inform Surveillance Using Electronic Health Records. *Prev Chronic Dis*. 2017;14:E44. doi:10.5888/pcd14.160516

28. Barker L, Rolka H, Rolka D, Brown C. Equivalence Testing for Binomial Random Variables. *Am Stat*. 2001;55(4):279-287. doi:10.1198/000313001753272213

29. Barker LE, Luman ET, McCauley MM, Chu SY. Assessing Equivalence: An Alternative to the Use of Difference Tests for Measuring Disparities in Vaccination Coverage. *Am J Epidemiol*. 2002;156(11):1056-1061. doi:10.1093/aje/kwf149

30. Lakens D. Equivalence Tests: A Practical Primer for t Tests, Correlations, and Meta-Analyses. *Soc Psychol Personal Sci*. 2017;8(4):355-362. doi:10.1177/1948550617697177

31. Lakens D, Scheel AM, Isager PM. Equivalence Testing for Psychological Research: A Tutorial. *Adv Methods Pract Psychol Sci*. 2018;1(2):259-269. doi:10.1177/2515245918770963

32. Hug L, You D, Blencowe H, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. *The Lancet*. 2021;398(10302):772-785. doi:10.1016/S0140-6736(21)01112-0

33. Matendo RM, Engmann CM, Ditekemena JD, et al. Challenge of Reducing Perinatal Mortality in Rural Congo: Findings of a Prospective, Population-based Study. *J Health Popul Nutr*. 2011;29(5):532-540.

34. Engmann C, Matendo R, Kinoshita R, et al. Stillbirth and early neonatal mortality in rural Central Africa. *Int J Gynecol Obstet*. 2009;105(2):112-117. doi:10.1016/j.ijgo.2008.12.012

35. McClure EM, Wright LL, Goldenberg RL, et al. The global network: a prospective study of stillbirths in developing countries. *Am J Obstet Gynecol*. 2007;197(3):247.e1-247.e5. doi:10.1016/j.ajog.2007.07.004

36. McClure EM, Saleem S, Goudar SS, et al. Stillbirth 2010–2018: a prospective, population-based, multi-country study from the Global Network. *Reprod Health*. 2020;17(2):146. doi:10.1186/s12978-020-00991-y

37. McClure E, Garces A, Saleem S, et al. Global Network for Women's and Children's Health Research: probable causes of stillbirth in low- and middle-income countries using a prospectively defined classification system. *BJOG Int J Obstet Gynaecol*. 2018;125(2):131-138. doi:10.1111/1471-0528.14493

38. Blencowe H, Krasevec J, Onis M de, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. 2019;7(7):e849-e860. doi:10.1016/S2214-109X(18)30565-5

39. Ngandu CB, Momberg D, Magan A, Norris SA, Said-Mohamed R. Association Between Household and Maternal Socioeconomic Factors with Birth Outcomes in the Democratic Republic of Congo and South Africa: A Comparative Study. *Matern Child Health J*. 2021;25(8):1296-1304. doi:10.1007/s10995-021-03147-x

40. Kangulu IB, Umba EKN, Nzaji MK, Kayamba PKM. Facteurs de risque de faible poids de naissance en milieu semi-rural de Kamina, République Démocratique du Congo. *Pan Afr Med J*. 2014;17(220). doi:10.11604/pamj.2014.17.220.2366

41. World Bank. *Democratic Republic of Congo Urbanization Review: Productive and Inclusive Cities for an Emerging Congo*. World Bank; 2018. doi:10.1596/978-1-4648-1203-3

42. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0

43. Milabyo Kyamusugulwa P. [Low birth weight in Maniema (Democratic Republic of Congo)]. *Sante Montrouge Fr*. 2006;16(2):103-107.

44. Kasonia K. Safety of the Ad26.Zebov, MVA-BN-Filo Ebola virus vaccine in pregnant women in an open-label clinical trial conducted during the 2018-2020 Ebola virus outbreak in the Democratic Republic of the Congo. Presented at: 2022 Annual Meeting of the American Society of Tropical Medicine & Hygiene; October 31, 2022; Seattle, USA.

45. Cao G, Liu J, Liu M. Global, Regional, and National Incidence and Mortality of Neonatal Preterm Birth, 1990-2019. *JAMA Pediatr*. 2022;176(8):787-796. doi:10.1001/jamapediatrics.2022.1622

46. Kramer MS, Papageorghiou A, Culhane J, et al. Challenges in defining and classifying the preterm birth syndrome. *Am J Obstet Gynecol*. 2012;206(2):108-112. doi:10.1016/j.ajog.2011.10.864

47. Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine*. 2016;34(49):6047-6056. doi:10.1016/j.vaccine.2016.03.045

48. Smid MC, Stringer EM, Stringer JSA. A Worldwide Epidemic: The Problem and Challenges of Preterm Birth in Low- and Middle-Income Countries. *Am J Perinatol*. Published online February 3, 2016:276-289. doi:10.1055/s-0035-1571199

49. Geerts L, Poggenpoel E, Theron G. A comparison of pregnancy dating methods commonly used in South Africa: a prospective study. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd*. 2013;103(8):552-556. doi:10.7196/samj.6751

50. Bengtson AM, Westreich D, Musonda P, et al. Multiple Overimputation to Address Missing Data and Measurement Error: Application to HIV Treatment During Pregnancy and Pregnancy Outcomes. *Epidemiol Camb Mass*. 2016;27(5):642-650. doi:10.1097/EDE.0000000000000494

51. Unintended Pregnancy and Abortion Among Adolescents in Kinshasa, Democratic Republic of Congo. Guttmacher Institute. Published November 23, 2021. Accessed January 19, 2023. https://www.guttmacher.org/fact-sheet/unintended-pregnancy-and-abortion-among-adolescents-kinshasa-democratic-republic-congo

52. Fatusi A, Riley T, Kayembe PK, Mabika C. Unintended pregnancy, induced abortion and abortion care-seeking experiences among adolescents in Kinshasa, Democratic Republic of Congo: a cross-sectional study. *BMJ Open*. 2021;11(9):e044682. doi:10.1136/bmjopen-2020-044682

53. Feng S, Hategeka C, Grépin KA. Addressing missing values in routine health information system data: an evaluation of imputation methods using data from the Democratic Republic of the Congo during the COVID-19 pandemic. *Popul Health Metr*. 2021;19(1):44. doi:10.1186/s12963-021-00274-z

54. Hoxha K, Hung YW, Irwin BR, Grépin KA. Understanding the challenges associated with the use of data from routine health information systems in low- and middle-income countries: A systematic review. *Health Inf Manag J*. 2022;51(3):135-148. doi:10.1177/1833358320928729

55. World Health Organization. First case of COVID-19 confirmed in the Democratic Republic of the Congo. WHO | Regional Office for Africa. Accessed January 10, 2022. https://www.afro.who.int/news/first-case-covid-19-confirmed-democratic-republic-congo

Chapter 3. The Impact of COVID-19 Mitigation Measures on Neonatal Health Outcomes in Kinshasa, Democratic Republic of the Congo: An Interrupted Time Series Analysis

3.1. Abstract

Research is mixed regarding the impact of COVID-19 mitigation measures on neonatal health outcomes; moreover, investigations on the topic within sub-Saharan Africa have been limited. In response, we compared the incidence of stillbirth, low birth weight (LBW), and preterm birth (PTB) before and after the introduction of mitigation measures in Kinshasa, Democratic Republic of the Congo (DRC). This retrospective cohort study utilized archival medical records from September 2019 to August 2020 to collect demographic and clinical variables on mothers and their newborns and employed interrupted time series (ITS) methodology. Mixed-effect segmented regression models comparing the pre-COVID-19 period to the COVID-19 mitigation measures period were used to generate incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs); time-varying confounders and seasonality were incorporated into the models as needed. Additionally, multiple imputation was performed to impute missing data. A total of 11,757 medical records were abstracted over the study period and aggregated at the health-facility-week level. Segmented regression models indicated that the stillbirth rate (adjusted IRR: 0.97; 95% CI: 0.94, 1.02) did not increase while the rates of LBW (adjusted IRR: 0.96; 95% CI: 0.94, 0.98) and PTB (adjusted IRR: 0.96; 95% CI: 0.94, 0.98) declined slightly during the COVID-19 mitigation measures period. This study succeeded in employing ITS methodology to assess the impact of COVID-19 mitigation measures on the incidence of select adverse birth outcomes in Kinshasa, DRC. Though issues were identified in our ability to properly assess seasonality, we hope that our findings provide practical insights for Congolese health officials regarding the real-world effects of COVID-19 mitigation measures during the first wave of the pandemic and enable

them to be better-prepared if similar policies need to be introduced in response to future infectious disease outbreaks.

3.2. Introduction

Since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in December 2019, the COVID-19 pandemic has strained health systems throughout the world and weakened global health infrastructures.[1] The pandemic as well as associated pandemic policies have also had deleterious effects on mental health,[2–4] the global economy and financial markets,[5,6] and food insecurity.[7–9] Additionally, in terms of the pandemic's global impact, the World Health Organization (WHO) estimates there have been approximately 760 million confirmed cases of COVID-19 (including nearly 7 million reported deaths) as of March 16, 2023.[10] In contrast to the high COVID-19 caseloads in other parts of the world, the WHO African Region has remained the least affected area with only 9.5 million (1.25%) confirmed cases of COVID-19 and 175,315 (2.55%) reported COVID-19 deaths as of March 16, 2023;[10] in the Democratic Republic of the Congo (DRC) specifically, there have been 95,814 confirmed cases with 1,464 associated deaths in the country as of March 16, 2023.[11]

The first case of COVID-19 in the DRC was reported on March 10, 2020;[12] in response, the national government immediately introduced outbreak management and control plans that included COVID-19 mitigation measures like the closure of bars, restaurants, and schools. On March 24, 2020, the Congolese government then declared a nationwide state of public health emergency that resulted in the closure of international borders, the restriction of travel in and out of the capital, Kinshasa, and the compulsory wearing of masks. In Kinshasa itself, the governor announced the total confinement of the municipality of Gombe (i.e., *La Gombe*), an affluent area where many key governing bodies are stationed, on April 6, 2020 in response to an outbreak of

COVID-19 cases in that area. The Gombe lockdown was partially lifted on April 22, 2020 but officially remained in place until June 29, 2020. The national state of public health emergency, on the other hand, was renewed six times and ultimately ended on July 22, 2020; however, Kinshasa did not begin to relax its COVID-19 mitigation measures until September 2020.[13–17]

Many feared that such measures would lead to decreased access to healthcare, particularly maternal and neonatal health services, as well as increased rates of adverse pregnancy and birth outcomes in the DRC and other low- and middle-income countries (LMICs).[18–20] Indeed, early investigations conducted in South Africa,[21] Pakistan,[22] and Nepal[23] suggested that lockdowns and other mitigation measures led to decreases in routine immunizations, institutional delivery rates, and/or the utilization of child healthcare services. Within the DRC though, a natural experimental analysis of District Health Information System 2 (DHIS2) data during the first wave of the pandemic in Kinshasa found that maternal health services and vaccinations were not significantly affected by the pandemic itself or by lockdown measures.[13] Somewhat similarly, research from eight sub-Saharan African countries (including the DRC) indicated that the most substantial reductions in medical services during the early stages of the pandemic were reported for outpatient consultations and childhood vaccinations, while results for reproductive and maternal healthcare service utilization were mixed.[24] Regarding adverse birth outcomes, Naqvi et al.[25] performed a prospective, population-based cohort study among pregnant women enrolled in the Global Network for Women's and Children's Health's Maternal and Newborn Health Registry in Kenya, Zambia, DRC, Pakistan, India, and Guatemala and reported no increases in stillbirth, neonatal mortality, maternal mortality, low birth weight (LBW), or preterm birth (PTB) during the COVID-19 period compared with the previous year.

Nonetheless, our overall comprehension of the public health impact of the COVID-19 pandemic on maternal and neonatal health outcomes is still evolving. Although the literature broadly supports an association between SARS-CoV-2 infection during pregnancy and certain adverse birth outcomes like PTB and stillbirth,[26–30] results have been more mixed with regards to the impact of COVID-19 mitigation measures on adverse birth outcomes. For example, one of the first meta-analyses conducted in this topic area that compared pregnancy and birth outcomes before and during the first wave of the pandemic reported increases in maternal deaths, stillbirth, ruptured ectopic pregnancies, and maternal depression; however, the authors noted that other outcomes showed considerable disparity between high- and low-resource settings.[31] Later meta-analyses produced conflicting results;[32–35] for instance, Vaccaro et al.[32] determined that lockdown measures were associated with a significantly increased risk of stillbirth but were not associated with PTB or LBW, while Hawco et al.[34] concluded that COVID-19 mitigation measures resulted in a reduction in PTB for iatrogenic births and in singleton pregnancies but had no effect on the risk of stillbirth or LBW. More recently, an interrupted time series (ITS) and meta-analysis using data from approximately 52 million births across 26 (mostly high-income) countries reported small reductions in PTB during the first three months of lockdowns; the authors also noted that there were somewhat mixed results for stillbirth due to it being a relatively rare event, thereby resulting in imprecise estimates.[36]

Despite the value of these studies, investigations specifically examining adverse pregnancy and birth outcomes during the early stages of the COVID-19 pandemic within sub-Saharan Africa have been relatively uncommon; for instance, little research has been conducted on the effect of COVID-19 mitigation measures on adverse birth outcomes in the DRC. In response to this knowledge gap, we built on preliminary research conducted by our group in this area[37] and compared the incidence of stillbirth, LBW, and PTB in the pre-COVID-19 period to the COVID-19 mitigation period in Kinshasa, DRC via ITS methodology. By assessing the association between pandemic policies and certain adverse birth outcomes in Kinshasa, we aimed to inform Congolese policymakers and health officials about the effects of such policies on neonatal health so that they are more knowledgeable in case they need to implement similar measures in response to future infectious disease outbreaks.

3.3. Methods

Study design & sites/procedures

This investigation was an observational study that utilized the previously mentioned retrospective cohort comprised of archival medical records abstracted from health facilities throughout Kinshasa; the overall study design, site selection, and data collection procedures have been described elsewhere.[37,38] Briefly though, we conducted a two-phase facility-based retrospective cohort study that first collected and digitized archival medical records of mother-child pairs from births occurring in delivery centers throughout Kinshasa between July 1, 2019 and February 28, 2020; in response to the COVID-19 pandemic, a second phase of data collection and digitization was performed on the archival medical records of mother-child pairs from births taking place in the same delivery centers between March 1, 2020 and August 31, 2020. For both rounds of data collection, abstractors first used Open Data Kit software to abstract necessary information and then uploaded the results to an online server; next, the results were downloaded and screened to identify deliveries that resulted in an adverse birth outcome. For those deliveries, a supplementary module to collect additional information on the mother was implemented. In order to be eligible for selection into this retrospective cohort, the health facilities had to have met the following inclusion criteria: presence of a maternity ward, high birth volume (i.e., more than 1000 births per year), and on-site storage of birth records. The ten study sites that were ultimately selected via random sampling were Bomoi, Bondeko, Lisanga, Siloe Bdom, and Bosembo Health Centers; Esengo, Mokali, Saint Joseph, and Kinshasa General Reference Hospitals; and Ngaliema Clinic.

Variables

The primary outcome variables of interest were the following: stillbirth, LBW, and PTB. Stillbirth was defined per standard practice (i.e., the birth of a baby following fetal death either before [antepartum stillbirth] or during labor or birth [intrapartum stillbirth])[39] and screened positive when there was any instance of either intra- or post-partum stillbirth in the archival medical records. Similarly, LBW was defined according to the WHO cutoff (i.e., a birth weight less than 2,500 grams),[40] and thus this cutoff was used to distinguish LBW newborns in the archival medical records. Likewise, PTB was identified via explicit PTB designation and/or presence of a gestational age at birth less than 37 completed weeks[41] in the archival medical records. Additionally, the initial imposition of COVID-19 mitigation measures (i.e., the imposition of mask mandates, social distancing policies, school/bar/restaurant closures, travel restrictions, etc.)[13,17] was considered the intervention/exposure of interest. With regards to time periods, September 17, 2019 through March 9, 2020 was classified as the pre-COVID-19 period (i.e., the "control" period) while March 10, 2020 through August 29, 2020 was classified as the COVID-19 mitigation measures period (i.e., the "treated" period); this time frame for the treated period was chosen in order to fully include the introduction and eventual phasing out of COVID-19 mitigation measures in Kinshasa.[12–17] Statistical considerations drove the time frame selection for the control period as statistical power is increased in ITS analyses when the number of time points are equally distributed pre- and post-intervention;[42] moreover, a common recommendation for ITS analyses is to have at least twelve time points before and after the intervention.[43–45]

Furthermore, the following variables were considered as covariates of interest due to their potential confounding effect for all analyses: newborn sex (i.e., male or female), maternal age (in years), delivery complications (i.e., documentation of antepartum/postpartum hemorrhage, a retained placenta, obstructed labor, and/or maternal death), singleton status (i.e., singleton or multiple birth), delivery type (i.e., vaginal delivery or Cesarean section), and parity (i.e., nulliparous [0 previous deliveries], multiparous [1 to 4 previous deliveries], or grand multiparous [5 to 10 previous deliveries]). The health facility in which the deliveries were performed was also recorded because the primary unit of observation was the health-facility week. Relatedly, date of birth (DOB) was used as the "running variable" to enable the observation of outcomes over time; for analysis purposes, DOBs were grouped into weekly intervals, thereby resulting in twenty-five time points before and after the intervention. As a DOB was necessary to accurately track the outcomes over time, any newborn without a DOB explicitly recorded in their medical record was not eligible for inclusion in the final study population. A hypothesized causal diagram depicting the relationships between the study variables can be found in Supplemental Figure 3.1.

Primary statistical analysis

For the comparison of stillbirth, LBW, and PTB between the pre-COVID-19 period and the COVID-19 mitigation period, a natural experimental approach was used and an ITS design – which is an established way to analyze "a sequence of count or continuous data at evenly spaced intervals over time, with one or more well-defined change points that correspond to the introduction of an intervention"[46] – informed the primary analytical approach. Since there are short-term outcomes that are expected to change relatively quickly in the post-intervention period, a clearly defined differentiation between the pre- and post-intervention periods, and sequential measures of the outcome both before and after the intervention, an ITS design was determined to be an appropriate analysis method for our purposes according to the recommendations from Bernal et al.[42] We hypothesized that the impact of the COVID-19 mitigation measures would result in a negative slope change for LBW and for PTB during the COVID-19 mitigation period; however, we hypothesized that there would be no change in either the slope or the trend level for stillbirth during the COVID-19 mitigation period.

Descriptive statistics were first generated at the individual level. Covariate information on the mothers and their newborns in both periods and overall were tabulated using means with standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables. Covariate balance between the two time periods of interest was assessed via Welch's two-sample *t*-test or Pearson's chi-squared test (as appropriate) at the 0.05 level of significance; any time-varying covariates (i.e., covariates that were significantly different between the two time periods) were considered as potential confounders. As our primary unit of observation was the health-facility week, descriptive statistics were also generated at this aggregated level to confirm that they were consistent with individual-level results. Covariate balance between the two time periods of interest was assessed at the aggregated level via visual inspection to confirm the balance/imbalance matched the individual-level findings. Time-varying covariates that were consistent across the individual- and aggregated-level results were designated as confounders. Additionally, graphical representations of the time series in weekly intervals for each adverse birth outcome were generated to visually assess the data (and ensure the suitability of the ITS approach).

For regression analyses, the following mixed-effect segmented regression model accounting for health-facility heterogeneity using health-facility-week-level counts of each adverse birth outcome (with total deliveries as the corresponding offset) was used to generate crude incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs):

$$E(Y_{i,t}|Time_t, Post_t) = e^{(\beta_{0i}+\beta_1 * Time_t+\beta_2 * Post_t+\beta_3 * Time_t * Post_t+\varepsilon_{i,t})},$$

where $Y_{i,t}$ was the incidence of the outcome of interest (i.e., either stillbirth, LBW, or PTB) at health facility i at time-point t, $Time_t$ was the time elapsed since the start of the study in weekly intervals at time-point t, $Post_t$ was a dummy variable for pre-intervention (i.e., $Post = 0$) and post-intervention (i.e., $Post = 1$) at time-point t, β_{0i} was the baseline incidence of the outcome of interest at $t = 0$ with a health-facility-level random effect, β_1 was the underlying pre-intervention trend, β_2 was the level change immediately following the intervention, β_3 was the slope (i.e., the trend) change following the intervention, and $\varepsilon_{i,t}$ was the error term. The following adjusted mixed-effect segmented regression model accounting for health-facility heterogeneity that incorporated the effect of the time-varying confounders using health-facility-week-level counts of each adverse birth outcome (with total deliveries as the corresponding offset) was used to generate adjusted IRRs with corresponding 95% CIs:

$$E\left(Y_{i,t}\middle|Time_t, Post_t, C_t\right) = e^{(\beta_{0i}+\beta_1 * Time_t+\beta_2 * Post_t+\beta_3 * Time_t * Post_t+\beta_4 * C_t+\varepsilon_{i,t})},$$

where C_t represented the time-varying confounders at time-point t and β_4 represented the effect of the time-varying confounders. A log-linear rate model, assuming a negative binomial distribution to account for overdispersion for each outcome, was used to inform all segmented regression models.

To account for the relatively short time series before and after the intervention, the seasonality of each outcome was incorporated into the segmented regression models as a time-varying confounder when necessary. No studies were identified in the literature that investigated the seasonality of stillbirth, LBW, and PTB in Kinshasa; thus, the previously discussed DHIS2 database – which is the world's largest health information management platform and was adopted by the DRC Ministry of Health as the national health information system beginning in 2014[47,48] – was used to determine whether any of these adverse birth outcomes exhibited seasonal variation in Kinshasa during the previous two years (i.e., from September 2017 through August 2019). For those outcomes that were determined to exhibit seasonal variation upon visual inspection, the corresponding segmented regression model was updated to account for the seasonality by the addition of periodic functions via Fourier terms, which is a common method to account for seasonality.[42,49,50] Visual inspection was used to assess the seasonality as opposed to formal statistical tests due to the fact that only a limited number of (monthly) observations were available from the DHIS2 data, thereby leading to inadequate statistical power. All segmented regression models were also assessed for autocorrelation (i.e., the phenomenon in which consecutive observations tend to be more similar to one another than those that are farther apart)[42,49] via the partial autocorrelation function (PACF).

Lastly, multiple imputation (MI) methods were employed to impute missing data at the individual level as some variables (e.g., parity, delivery complications, and maternal age) had moderate levels of missingness (i.e., ranging from 10% to 25%) while other variables (e.g., newborn sex and LBW) had minor levels of missingness (i.e., less than 5%). After inspection of the possible missing data-generating mechanisms, it was determined that the missingness pattern was dependent on health-facility type (i.e., hospital vs. health center vs. clinic) with Ngaliema Clinic contributing the highest levels of missingness (i.e., greater than 50%) for parity, delivery complications, and maternal age (Supplemental Figure 3.2). Therefore, we assumed that the data were missing at random (MAR) and utilized the MI by chained equations (MICE) procedure.[51,52] More specifically, we generated ten multiply imputed datasets using the *mice* package[51] with a seed of 976 and included the following variables in the MICE procedure: maternal age, parity, delivery complications, delivery type, singleton status, newborn sex, stillbirth, LBW, PTB, and health-facility type. To impute maternal age, we used predictive mean matching, while polynomial regression was used for imputing parity. The remaining variables (except health-facility type, which was completely observed) were all imputed using logistic regression. The results of the MICE procedure were also evaluated to ensure that none of the imputations were markedly different from the observed data.

Sensitivity analyses

Furthermore, a number of sensitivity analyses were performed. First, in order to account for any potential delays in effect, a sensitivity analysis, in which a two-week buffer period was added after the imposition of COVID-19 mitigation measures, was conducted; for this sensitivity analysis, the pre-COVID-19 period remained the same (i.e., from September 17, 2019 through March 9, 2020), but the COVID-19 mitigation period was changed from March 10, 2020 through August 29, 2020 to March 24, 2020 through August 29, 2020. Second, in order to account for potential effects related to time period selection bias (which has been documented as a critique of other studies in this area),[53] another sensitivity analysis, in which the pre-COVID-19 mitigation period was extended, was conducted; for this sensitivity analysis, the pre-COVID-19 period was changed from September 17, 2019 through March 9, 2020 to July 1, 2019 through March 9, 2020, while the COVID-19 mitigation period remained the same (i.e., from March 10, 2020 through August 29, 2020). Third, in order to account for the fact that Kinshasa had a partial lockdown in only one part of the city (i.e., Gombe),[13–17] a final sensitivity analysis, in which the ITS procedure was stratified by lockdown status, was conducted; for this sensitivity analysis, the two health facilities located within Gombe (i.e., Ngaliema Clinic & Kinshasa General Reference Hospital) were considered as the lockdown health facilities while the other eight health facilities were considered the non-lockdown health facilities. All statistical analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Informed consent and ethical approval

No informed consent process took place as no active participant recruitment or enrollment were performed. Institutional review board (IRB) approval was obtained from the University of California, Los Angeles (IRB#19-002150) as well as the Kinshasa School of Public Health at the University of Kinshasa (ESP/CE/300/2019), which served as the local ethics committee, to perform the retrospective data collection/analysis procedures. Additionally, the use/analysis of the DHIS2 for seasonality background information met the criteria for exemption from IRB review due to the fact that the DHIS2 data are de-identified, secondary data.

3.4. Results

Study population

A total of 11,757 medical records with DOB information were abstracted over the study period with 5,457 medical records (46.41%) abstracted during the pre-COVID-19 period and 6,300 medical records (53.59%) abstracted during the COVID-19 mitigation measures period. Mean maternal age was 28.74 years (SD: 6.33 years); more than three-quarters (i.e., 81.92%) of the deliveries were vaginal deliveries and the vast majority (i.e., 94.79%) of the deliveries resulted in a singleton birth. Moreover, only 6.18% of the women were grand multiparous, while 31.32% and 62.50% were nulliparous and multiparous, respectively. When stratified by treatment period, we saw that slightly more males were born during the COVID-19 mitigation measures period (i.e., 53.13% vs. 51.15%, unadjusted *p*-value = 0.033); additionally, delivery complications were much less common during the COVID-19 mitigation measures period (i.e., 22.16% vs. 31.83%, unadjusted *p*-value < 0.001). Regarding the adverse birth outcomes of interest, there was virtually no difference in the proportion of stillbirth or LBW across treatment periods; however, there was a slightly lower proportion of PTB during the COVID-19 mitigation measures period (i.e., 9.14% vs. 10.28%, unadjusted *p*-value = 0.04) (Table 3.1).

Aggregated data assessments

When aggregated at the health-facility-week level, covariate balance was found to be consistent with the individual-level results. For example, the mean maternal age and the proportions of singleton deliveries, vaginal deliveries, and multiparous women were still non-differential across treatment periods; likewise, we again saw that there was a slightly higher proportion of male newborns but a much lower proportion of delivery complications in the COVID-19 mitigation measures period compared to the pre-COVID-19 period (Figure 3.1). Thus, newborn sex and delivery complications were considered as time-varying confounders for the adjusted segmented regression models. Furthermore, plots of the time series in weekly intervals suggested declines in the LBW and PTB rates during the COVID-19 mitigation measures period; however, no change in the stillbirth rate appeared to occur during the COVID-19 mitigation measures period based on the time series plot (Figure 3.2).

Seasonality evaluations

Seasonality evaluations yielded mixed results. For instance, visual inspection of the monthly time series data from the DHIS2 for all three adverse birth outcomes suggested a peak around December through February with a corresponding decline beginning in March or April in each evaluated annual period; however, these peaks and declines for stillbirth and PTB were all within one or two percentage points, while the peaks and declines for LBW were within a much wider range (i.e., around six percentage points). Moreover, examination of the 95% CIs and standard error around the trend lines indicated that there were high (but not complete) levels of overlap across the months within a given a year (Figure 3.3). Thus, a clear seasonal pattern was not established for any of the three adverse birth outcomes of interest; nonetheless, since all three outcomes suggested a decline in March or April (and March 10th represented the threshold between the pre-COVID-19 and COVID-19 mitigation periods), a conservative approach was taken in which adjusted segmented regression models were further modified via the addition of a single sine/cosine pair in order to incorporate the (potentially) confounding effect of seasonality.

Primary ITS analyses

In the crude segmented regression models, we found that the rate of stillbirth was unchanged – or at the very least, did not increase – during the COVID-19 mitigation measures period (IRR: 0.97; 95% CI: 0.94, 1.01); however, the crude segmented regression models also demonstrated that the rates of LBW (IRR: 0.96; 95% CI: 0.94, 0.98) and PTB (IRR: 0.97; 95% CI: 0.94, 0.99) declined slightly during the COVID-19 mitigation measures period. Additionally, the crude segmented regression models showed that the underlying pre-intervention rates of stillbirth and PTB were essentially static (as the corresponding IRRs for both outcomes was 1.00), while the underlying pre-intervention LBW rate was slightly positive (IRR: 1.02; 95% CI: 1.00, 1.03). Regarding the level change following the imposition of COVID-19 mitigation measures, results were mixed by outcome (Table 3.2); however, it should be noted that any change (or lack thereof) in the week following the imposition of COVID-19 mitigation measures was more likely due to underlying variability in the time series itself as opposed to any immediate effect of the imposition of COVID-19 mitigation measures.

After adjusting for delivery complications and newborn sex (i.e., the time-varying confounders) in the adjusted segmented regression models, the results were virtually unchanged. For instance, the slope changes for stillbirth (IRR: 0.97; 95% CI: 0.94, 1.02), LBW (IRR: 0.96; 95% CI: 0.94, 0.98), and PTB (IRR: 0.96; 95% CI: 0.94, 0.98) following the imposition of the COVID-19 mitigation measures in the adjusted model were almost identical to the corresponding slope changes from the crude model. However, after also accounting for potential seasonality, the results were slightly altered. More specifically, the seasonality-adjusted model indicated that there was no change in the PTB rate (IRR: 0.94; 95% CI: 0.83, 1.05) during the COVID-19 mitigation measures period; however, the seasonality-adjusted model also indicated the lack of any change for the stillbirth rate but a decline in the LBW rate during the COVID-19 mitigation measures period, a finding consistent with the other two models (Table 3.2). Additionally, across all three model types (i.e., the crude, adjusted, and seasonality-adjusted models), PACF plots revealed that autocorrelation was not present (Figure 3.4), thereby confirming the independence of the observations and thus providing evidence for the validity of the ITS approach implemented here.

Sensitivity analyses

The results from both the first sensitivity analysis (i.e., the analysis that added a two-week lag after the imposition of COVID-19 mitigation measures) and the second sensitivity analysis (i.e., the analysis that extended the pre-COVID-19 period to July 2019) were essentially the same as the results from the primary ITS analysis. Somewhat similarly, in the third sensitivity analysis (i.e., the analysis that stratified the results by lockdown status), we did not detect any major differences between the health facilities located in the Gombe lockdown zone and the health facilities located outside of the lockdown zone in the crude and adjusted models (and these results were consistent with the results from the primary ITS analysis). However, it should be noted that the seasonality-adjusted models suggested differences in the post-intervention slope changes for stillbirth and PTB by lockdown status; nonetheless, these results were not statistically significant (Supplemental Table 3.1).

3.5. Discussion

Summary

This study utilized a natural experimental approach to evaluate the impact of COVID-19 mitigation measures during the first wave of the pandemic on three key adverse birth outcomes (i.e., stillbirth, LBW, and PTB) in Kinshasa, DRC via archival medical records. Through this ITS analysis, we determined that the stillbirth rate appeared to not increase while the LBW and PTB rates seemed to decline slightly after the imposition of COVID-19 mitigation measures. Despite issues in our ability to definitively assess the seasonality of the adverse birth outcomes using DHIS2 data, our results still provide critical insights into how COVID-19 policies affected neonatal health in the DRC; additionally, this investigation helps to address a fundamental knowledge gap regarding the effects of the COVID-19 pandemic within the DRC specifically and sub-Saharan Africa more generally.

Literature comparisons

As previously mentioned, there has yet to be a global consensus on the association between COVID-19 policies and perinatal health outcomes due to inconsistent results from a variety of studies, thereby making it challenging to draw broad conclusions or generalize findings across populations. For example, research from Argentina,[54] Botswana,[55] Denmark,[56,57] France,[58,59] Iceland,[60] Ireland,[61] Israel,[62] Italy,[63] Japan,[64] South Korea,[65] and the United States (US)[66,67] reported that the PTB rate decreased during periods when lockdowns and/or mitigation measures were in place compared to pre-COVID-19 periods, while other studies conducted in Austria,[68] Canada,[69,70] China,[71] England,[72] Jordan,[73] Spain,[74] Sweden,[75] Uganda,[76] and the US[77–79] did not detect any changes in the PTB rate during periods when lockdowns and/or mitigation measures were implemented; other studies in China[80] and Nepal[23] even concluded that the PTB rate increased after the imposition of mitigation measures. Similar discrepancies have been documented for stillbirth and LBW as evinced by the aforementioned meta-analyses conducted in this area.[31–34] Although the exact mechanism of any potential decrease in adverse birth outcome rates is unknown, some researchers have posited that the overall reduction in infectious disease incidence and decreased exposure to air pollution as a result of mitigation measures may all contribute.[36,55,81] Nonetheless, others have argued that methodological issues (e.g., a small number of outcomes and uncontrolled confounding) as well as the potential of publication bias undermine our ability to draw (causal) conclusions.[53,82]

Further complicating our comprehension, few studies have included both PTB and stillbirth rates in their analyses, thereby making it difficult to conclude whether any reduction in the PTB rate was potentially offset by a corresponding increase in the stillbirth rate.[36] In response to this knowledge gap, Calvert et al.[36] performed a large-scale ITS and meta-analysis using data from approximately 52 million births across 26 (mostly high-income) countries and found that the "decrease in PTBs did not appear to be linked with an increase in stillbirths in most settings." Though our analysis was conducted in a low-income setting, our results generally agreed with their findings in that we also found a reduction in the PTB rate without a corresponding increase in the stillbirth rate. Indeed, we even reported a similar change in the PTB rate as Calvert et al.[36] observed a 3–4% relative reduction, a finding in line with the IRRs of 0.97 of 0.96 reported here from the crude and adjusted models, respectively; likewise, although the PTB estimate from the seasonality-adjusted model was not statistically significant according to the classical threshold, its 95% CIs were still mostly compatible with a reduction in the PTB rate. Additionally, it should be highlighted that our results consistently suggested a reduction in LBW rates (across all three model types in the primary analysis) during the COVID-19 mitigation measures period. Although there is much less literature available on this topic, investigations conducted in Ireland,[83] South Korea,[65] and Uganda[76] also reported reductions in LBW during the imposition of COVID-19 mitigation measures; nonetheless, other studies from Spain,[74] Japan,[84] and Nepal[23] reported a lack of any such association.

Kinshasa-specific contextual considerations

Despite the commonalities between our findings and those from other studies, there are a few key considerations specific to Kinshasa that should be noted when contextualizing these results. First, research on adherence to COVID-19 prevention measures in Kinshasa has been mixed; for example, an online survey that enrolled 830 participants in Kinshasa from April 23 to June 8, 2020 reported high levels (i.e., ≥ 80%) of self-reported physical distancing, face mask use, and regular handwashing.[85] Nonetheless, a community-based cross-sectional study conducted in Kinshasa in June 2020 among 1326 participants concluded that most participants found wearing masks acceptable and reported doing so regularly along with handwashing but also reported that about half of the participants had low knowledge scores about COVID-19 transmission, signs/symptoms, and preventive measures.[86] Somewhat similarly, a cross-sectional study among 934 pregnant women in Kinshasa conducted between August 2020 and January 2021 employed direct observation to determine face mask adherence and concluded that overall and correct face mask adherence levels were low (i.e., 33.1% and 10.7%, respectively) among participants.[87] Therefore, it could be the case that the effect of the intervention (i.e., COVID-19 mitigation measures) was weaker in Kinshasa – due to low levels of adherence – than the interventions employed in other countries with higher levels of adherence/compliance, potentially suggesting that the reduction in PTB and LBW rates in Kinshasa could have been greater had adherence to COVID-19 mitigation measures been higher.

In a similar vein, the majority of the studies in this area were conducted in locations that experienced total lockdowns during the first wave of COVID-19, as such strategies were common in areas that experienced rapid increases in COVID-19 incidence. However, the local government in Kinshasa only implemented a partial lockdown in the municipality of Gombe as opposed to a city-wide lockdown.[13–17] As a result, the majority of the city only experienced general COVID-19 mitigation measures (such as mask wearing and basic social distancing); therefore, any cross-country comparisons should be made with caution as the type and degree of COVID-19 mitigation measures in Kinshasa were not necessarily equivalent to those from other countries, especially high-income ones. Nonetheless, it should be highlighted that our third sensitivity analysis (i.e., the analysis in which the results were stratified by lockdown status) was conducted in order to determine whether the Gombe lockdown resulted in significant differences for the health facilities in Gombe. Since those results did not suggest any discrepancies, it may be the case that the Gombe lockdown had spillover effects (which occur when "some aspect of [a] policy spills over and influences" outcomes in policy-unaffected areas)[88,89] that impacted the rest of the city; alternatively, since one of the only two Gombe health facilities in our sample was Kinshasa General Reference Hospital, it could also be the case that it was not possible to isolate the effect of the Gombe lockdown due to the fact that pregnant women from all over the city were eligible to be referred to Kinshasa General Reference Hospital (as highlighted by Hategeka et al.[13] in their analysis of health service utilization during the first pandemic wave in Kinshasa).

Furthermore, another major difference between this analysis and the ones conducted in other (high-income) countries relates to reported COVID-19 incidence. As previously mentioned, there have been only about 10,000 confirmed COVID-19 cases in the DRC as of March 16, 2023,[11] thereby suggesting a low overall SARS-CoV-2 infection rate throughout the DRC. However, recent serosurveillance analyses have demonstrated that "a key reason for low case burden in many African nations is significant underdetection and underreporting;"[90] indeed, a cross-sectional, household-based serosurvey conducted between October 2020 and November 2020 in Kinshasa among 1233 participants found that the estimated SARS-CoV-2 infection-to-case ratio was 292:1, thus demonstrating that the prevalence of SARS-CoV-2 was much higher in Kinshasa than the number of COVID-19 cases reported.[91] As a result of this imperfect picture of SARS-CoV-2 infection, it is difficult to determine how effective the mitigation measures were at reducing COVID-19 incidence in Kinshasa; the lack of such information thus further hinders our ability to fully contextualize our results (and perform direct international comparisons regarding the effect of mitigation measures on neonatal health outcomes) since SARS-CoV-2 infection during pregnancy is associated with an increased risk of PTB and stillbirth.[26–30]

Public health implications

Despite these caveats regarding the Kinshasa-specific context, our results still provide key insights for both Congolese and global health policymakers regarding the impact of COVID-19 mitigation measures on neonatal health outcomes in the DRC. More specifically, although the first wave of the COVID-19 pandemic was approximately three years ago, our findings have significant implications for public health responses to potential future outbreaks of other infectious diseases in the DRC (such as cholera, measles, malaria, and Ebola virus disease)[92,93] that may require the introduction of similar mitigation measures. For instance, in place of universal social distancing and/or mask wearing that can be difficult to promote/enforce, our results suggest that Congolese health officials could instead target their (limited) resources at pregnant women and actively promote the additional benefits of handwashing/mask wearing during pregnancy, thereby potentially increasing compliance, reducing overall case numbers, and improving maternal and neonatal health outcomes. Moreover, public health officials in the DRC could use this information to help health facilities better manage their staffing and resource allocation during mitigation periods so that critical personnel and support could be allocated to systems that were negatively impacted by the introduction of such measures instead of maternal and neonatal health services. Outside of the DRC, our results also add to the global knowledge base regarding the association between COVID-19 mitigation measures and neonatal health outcomes and provide critical information regarding the effects of the COVID-19 pandemic within sub-Saharan Africa.

Strengths and limitations

In support of our findings, the major strength of this study was the use of natural experimental methods to answer the research questions of interest. As a causal inference tool, the ITS procedure is generally considered one of the strongest methods for assessing interventions when randomization is not possible.[94,95] Furthermore, the very nature of the ITS design controls for the effect of secular trends in a time series of outcome estimates and allows researchers to visually assess the longitudinal impact of an intervention; additionally, the ITS design measures the real-world impact of an intervention, thereby increasing its external validity.[94,95] Likewise, the inclusion of several sensitivity analyses accounting for potential biases associated with our approach (such as time period selection bias) provided additional credence to the results from the primary ITS analysis. Another strength was the utilization of MI methods to account for incompletely observed data as this approach was more valid than other *ad hoc* approaches to missing data (such as complete case analysis) that can waste potentially valuable data points.[96] Additionally, the study setting (i.e., the DRC) represented another strength of this analysis due to the fact that the burden of adverse birth outcomes is much higher in sub-Saharan Africa than in other regions of the world; for example, a systematic assessment of global stillbirths from 2000 to 2019 concluded that sub-Saharan Africa had the highest stillbirth rates in 2019.[39] Thus, this high adverse birth outcome rate allowed for the detection of any minor changes during the imposition of COVID-19 mitigation measures.

However, there are several limitations of this investigation that must also be considered. For example, the archival medical records that were used to inform the analysis were not designed as research tools and thus may have contained data elements that are incorrectly classified, poorly specified, and/or missing;[97,98] although the MI procedure aided in addressing this limitation, it would not have been able to remedy any potential problems associated with misclassified data elements. Moreover, the results of this study may not be generalizable outside of Kinshasa; therefore, any conclusions made about the association between COVID-19 mitigation measures and neonatal health outcomes may not necessarily apply to other large urban areas in the DRC. Somewhat relatedly, our analysis only included deliveries that occurred in larger health facilities with on-site storage of birth records; as a result, home births and deliveries that occurred in smaller/less developed health facilities were excluded, potentially leading to the introduction of selection bias (assuming that home births/other institutional deliveries had a differential risk of adverse birth outcomes occurrence). Additionally, though the ITS method provides a solid basis for causal inference, it can still fall victim to the limitations of standard observational studies, such as uncontrolled confounding; indeed, due to the use of archival medical records for this analysis, we were not able to account for certain potential confounders, such as maternal education and socioeconomic status.

Furthermore, through the aggregation of our data at the health-facility-week level, we were only able to make observations about how COVID-19 mitigation measures impacted adverse birth outcome rates at the ecological level (as opposed to the individual level); nonetheless, it should be noted that individual-level analyses were attempted but were ultimately deemed infeasible due to excessively high levels of autocorrelation in the individual-level data. Lastly, limitations in our ability to accurately assess the seasonality of the adverse birth outcomes within Kinshasa using the DHIS2 database may have led us to incorrectly include seasonality-adjusted models, thereby adding unnecessary bias to our results. In order to mitigate this issue in future investigations examining policy impacts on neonatal health outcomes, alternative data sources for seasonality evaluations should be explored. Additionally, considering the relevance of seasonality information across a range of health domains, the completion of independent studies focused solely on understanding the seasonality of adverse birth outcomes in Kinshasa should be promoted as such investigations may yield important insights for public health in and of itself.

Conclusion

Notwithstanding these limitations, this study succeeded in employing ITS methodology to assess the impact of COVID-19 mitigation measures on the incidence of select adverse birth outcomes (i.e., stillbirth, LBW, and PTB) in Kinshasa, DRC. Our results suggested that the stillbirth rate did not increase while the LBW and PTB rates did slightly decrease after the imposition of COVID-19 mitigation measures, though issues were identified in our ability to properly assess the seasonality of the adverse birth outcomes. Nonetheless, we hope that our findings provide practical insights for Congolese health officials and policymakers regarding the real-world effects of COVID-19 mitigation measures during the first wave of the pandemic and enable them to be better-prepared if similar policies need to be introduced in response to future infectious disease outbreaks.

3.6. Tables and Figures

Table 3.1. Clinical and demographic characteristics of mothers and their newborns, overall and by treatment period

Characteristic	**Overall**	**Pre-COVID-19 Period**	**COVID-19 Mitigation Measures Period**	***Unadjusted p*-value****
	*N = 11,757**	*N = 5457**	*N = 6300**	
Health Facility				
Bomoi Health Center	1586 (13.49%)	682 (12.50%)	904 (14.35%)	<0.001
Bondeko Health Center	1228 (10.44%)	508 (9.31%)	720 (11.43%)	
Bosembo Health Center	533 (4.53%)	248 (4.54%)	285 (4.52%)	
Esengo General Hospital	1143 (9.72%)	527 (9.66%)	616 (9.78%)	
Kinshasa General Reference Hospital	1082 (9.20%)	486 (8.91%)	596 (9.46%)	
Lisanga Health Center	1500 (12.76%)	667 (12.22%)	833 (13.22%)	
Mokali General Hospital	747 (6.34%)	342 (6.27%)	405 (6.43%)	
Ngaliema Clinic	1700 (14.46%)	874 (16.02%)	826 (13.11%)	
Saint Joseph General Hospital	1300 (11.06%)	728 (13.34%)	572 (9.08%)	
Siloe Bdom Health Center	938 (7.97%)	395 (7.24%)	543 (8.62%)	
Parity				
Grand Multiparous	727 (6.18%)	366 (6.71%)	361 (5.73%)	0.079
Multiparous	7348 (62.50%)	3404 (62.38%)	3944 (62.60%)	
Nulliparous	3682 (31.32%)	1687 (30.91%)	1995 (31.67%)	
Delivery Type				
Cesarean Section	2126 (18.08%)	998 (18.29%)	1128 (17.90%)	0.6
Vaginal Delivery	9631 (81.92%)	4459 (81.71%)	5172 (82.10%)	
Singleton Status				

Characteristic	**Overall**	**Pre-COVID-19 Period**	**COVID-19 Mitigation Measures Period**	***Unadjusted p*-value****
	*N = 11,757**	*N = 5457**	*N = 6300**	
Singleton Birth	11,144 (94.79%)	5172 (94.78%)	5972 (94.79%)	>0.9
Multiple Birth	613 (5.21%)	285 (5.22%)	328 (5.21%)	
Newborn Sex				
Female	5619 (47.79%)	2666 (48.85%)	2953 (46.87%)	0.033
Male	6138 (52.21%)	2791 (51.15%)	3347 (53.13%)	
Delivery Complications				
Yes	3133 (26.6%)	1737 (31.83%)	1396 (22.16%)	<0.001
No	8624 (73.4%)	3720 (68.17%)	4904 (77.84%)	
Maternal Age (Years)	28.74 (6.33)	28.77 (6.39)	28.72 (6.28)	0.5
Stillbirth				
Yes	429 (3.65%)	210 (3.85%)	219 (3.48%)	0.3
No	11,328 (96.45%)	5247 (96.15%)	6081 (96.52%)	
LBW				
Yes	1555 (13.23%)	743 (13.62%)	812 (12.89%)	0.3
No	10,202 (86.77%)	4714 (86.38%)	5488 (87.11%)	
PTB				
Yes	1137 (9.67%)	561 (10.28%)	576 (9.14%)	0.04
No	10,620 (90.33%)	4896 (89.72%)	5724 (90.86%)	

*n (%), mean (standard deviation). **Pearson's Chi-squared test, Welch's Two Sample t-test. LBW = low birth weight, PTB = preterm birth.

Table 3.2. Results of the primary ITS analyses, by model type and by adverse birth outcome

Outcome	Parameters	Crude Model		Adjusted Model*		Seasonality-Adjusted Model**	
		IRR	95% CI	IRR	95% CI	IRR	95% CI
Stillbirth	Underlying pre-intervention trend	1.00	(0.98, 1.02)	1.00	(0.98, 1.03)	1.02	(0.94, 1.10)
	Level change following intervention	1.33	(0.87, 2.04)	1.32	(0.86, 2.02)	1.09	(0.60, 1.95)
	Slope change following intervention	0.97	(0.94, 1.01)	0.97	(0.94, 1.02)	0.95	(0.81, 1.11)
LBW	Underlying pre-intervention trend	1.02	(1.00, 1.03)	1.01	(1.00, 1.03)	1.03	(0.99, 1.08)
	Level change following intervention	1.24	(0.97, 1.58)	1.23	(0.97, 1.57)	0.86	(0.61, 1.21)
	Slope change following intervention	0.96	(0.94, 0.98)	0.96	(0.94, 0.98)	0.92	(0.84, 1.00)
PTB	Underlying pre-intervention trend	1.00	(0.98, 1.01)	1.00	(0.98, 1.01)	0.97	(0.92, 1.03)
	Level change following intervention	1.61	(1.19, 2.18)	1.60	(1.18, 2.16)	0.94	(0.62, 1.42)
	Slope change following intervention	0.97	(0.94, 0.99)	0.96	(0.94, 0.98)	0.94	(0.83, 1.05)

*Crude model + delivery complications and newborn sex. **Adjusted model + Fourier terms accounting for (potential) seasonality.
CI = confidence interval, IRR = incidence rate ratio, ITS = interrupted time series, LBW = low birth weight, PTB = preterm birth.

Figure 3.1. Covariate balance assessment across treatment periods at the aggregated level

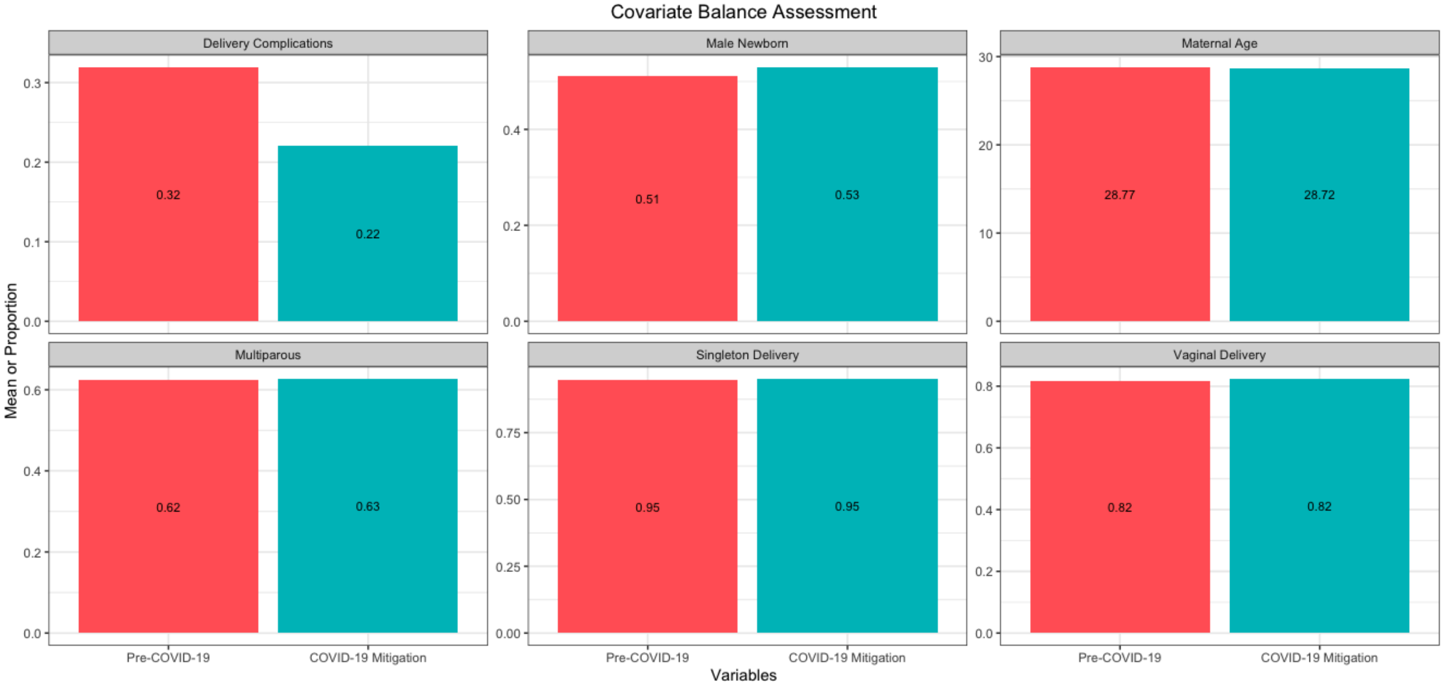


Figure 3.2. Time series in weekly intervals for each adverse birth outcome, stratified by treatment period

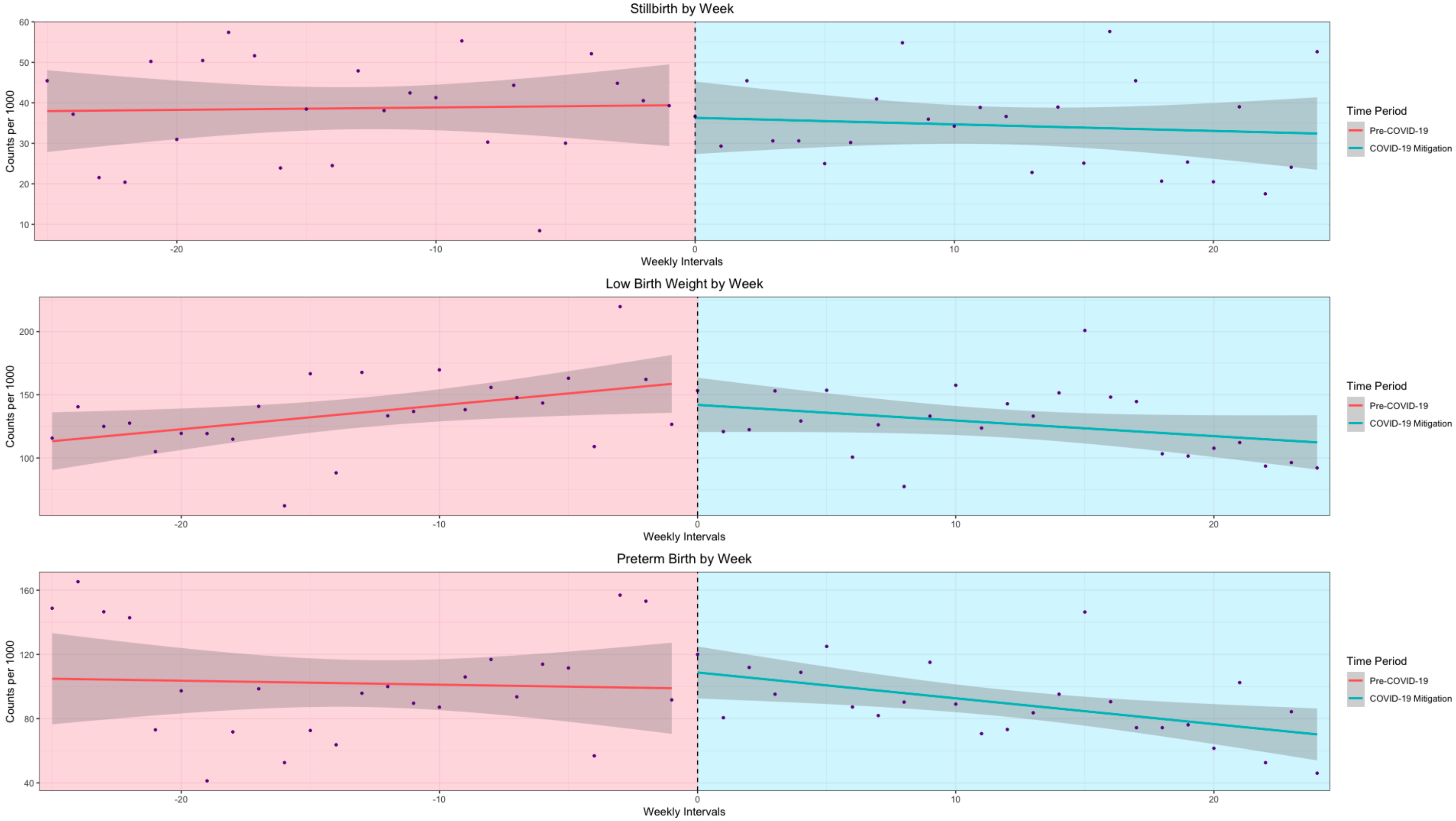
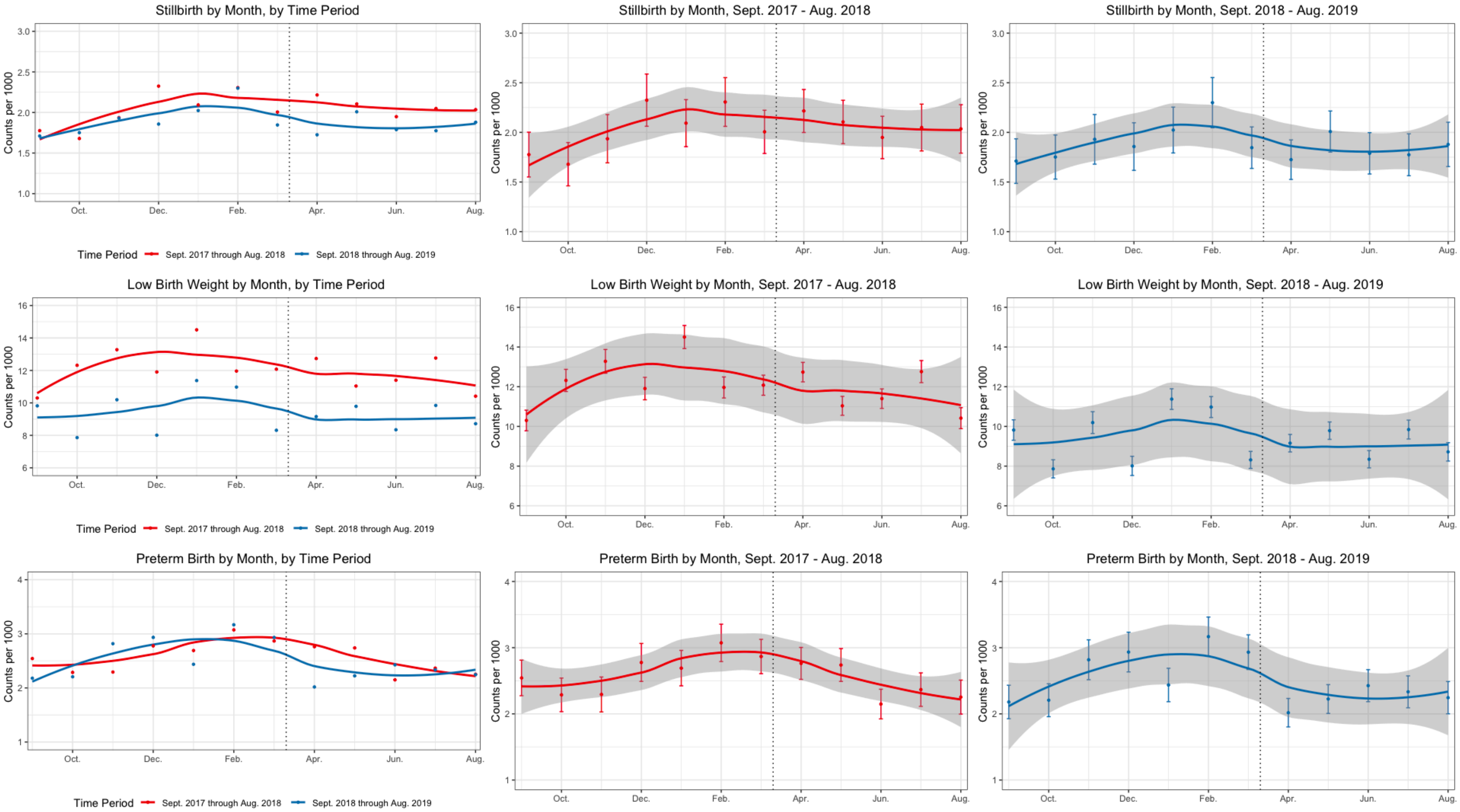


Figure 3.3. Seasonality assessment for each adverse birth outcome


Stillbirth by Month, by Time Period

Stillbirth by Month, Sept. 2017 - Aug. 2018

Stillbirth by Month, Sept. 2018 - Aug. 2019

Low Birth Weight by Month, by Time Period

Low Birth Weight by Month, Sept. 2017 - Aug. 2018

Low Birth Weight by Month, Sept. 2018 - Aug. 2019

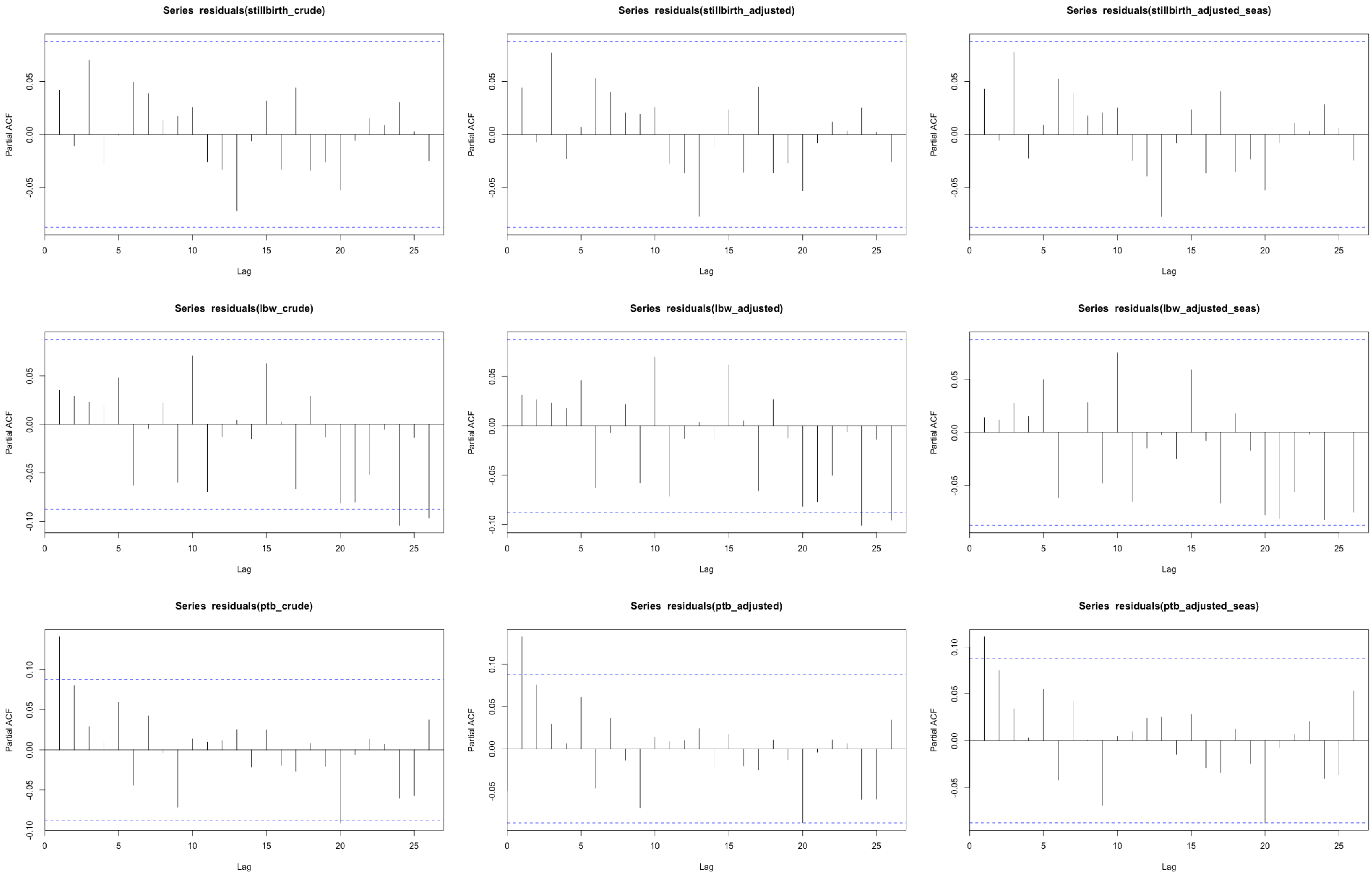
Preterm Birth by Month, by Time Period

Preterm Birth by Month, Sept. 2017 - Aug. 2018

Preterm Birth by Month, Sept. 2018 - Aug. 2019

Dotted line represents March 10th (i.e., the date corresponding to the introduction of COVID-19 mitigation measures in 2020).

Figure 3.4. Partial autocorrelation functions for the primary statistical analyses



ACF = autocorrelation function, LBW = low birth weight, PTB = preterm birth, seas = seasonality.

3.7. Appendix

Supplemental Table 3.1. Results of the sensitivity analyses, by model type and by adverse birth outcome

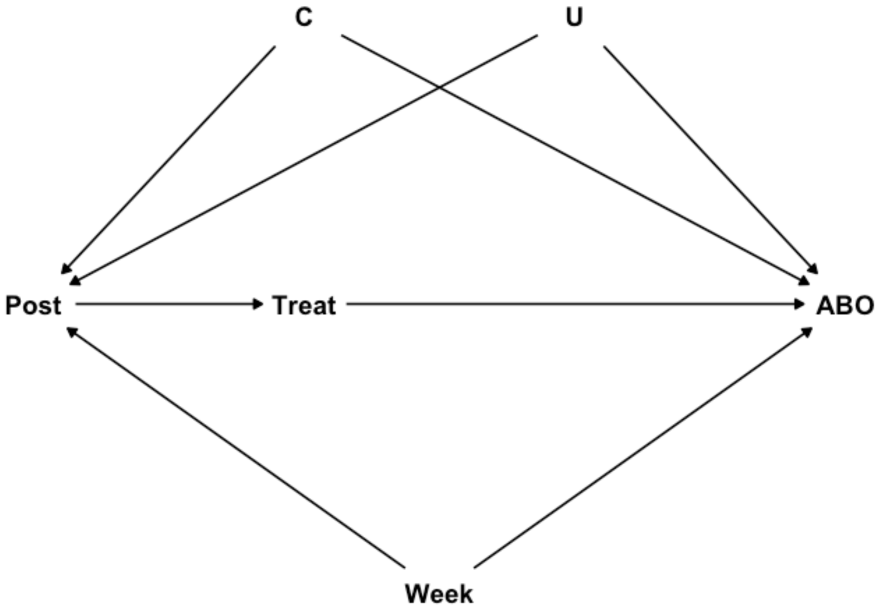
Sensitivity Analysis #1 - Addition of Two-Week Lag After Imposition of COVID-19 Mitigation Measures							
Outcome	**Parameters**	**Crude Model**		**Adjusted Model***		**Seasonality-Adjusted Model****	
		IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Stillbirth	Underlying pre-intervention trend	1.00	(0.98, 1.01)	1.00	(0.98, 1.03)	1.02	(0.94, 1.11)
	Level change following intervention	1.43	(0.89, 2.30)	1.42	(0.89, 2.28)	1.23	(0.62, 2.47)
	Slope change following intervention	0.97	(0.94, 1.00)	0.97	(0.93, 1.00)	0.93	(0.79, 1.10)
LBW	Underlying pre-intervention trend	1.02	(1.00, 1.03)	1.01	(1.00, 1.03)	1.04	(0.99, 1.09)
	Level change following intervention	1.31	(1.00, 1.72)	1.31	(1.00, 1.71)	0.89	(0.60, 1.33)
	Slope change following intervention	0.96	(0.94, 0.97)	0.96	(0.94, 0.97)	0.91	(0.83, 1.01)
PTB	Underlying pre-intervention trend	1.00	(0.98, 1.03)	1.00	(0.98, 1.02)	0.97	(0.91, 1.03)
	Level change following intervention	1.75	(1.26, 2.45)	1.74	(1.25, 2.44)	0.91	(0.56, 1.49)
	Slope change following intervention	0.96	(0.94, 0.98)	0.96	(0.94, 0.98)	0.90	(0.78, 1.02)
Sensitivity Analysis #2 - Extension of Pre-COVID-19 Period to July 2019							
Outcome	**Parameters**	**Crude Model**		**Adjusted Model***		**Seasonality-Adjusted Model****	
		IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Stillbirth	Underlying pre-intervention trend	1.01	(1.00, 1.03)	1.01	(1.00, 1.03)	1.02	(1.00, 1.03)
	Level change following intervention	1.19	(0.80, 1.76)	1.19	(0.81, 1.76)	0.81	(0.46, 1.40)
	Slope change following intervention	0.96	(0.94, 0.99)	0.96	(0.94, 0.99)	0.98	(0.95, 1.01)

LBW	Underlying pre-intervention trend	1.01	(1.00, 1.02)	1.01	(1.00, 1.02)	1.01	(1.00, 1.02)
	Level change following intervention	1.31	(1.05, 1.64)	1.31	(1.05, 1.64)	1.45	(1.06, 1.98)
	Slope change following intervention	0.97	(0.95, 0.98)	0.97	(0.95, 0.98)	0.96	(0.95, 0.98)
PTB	Underlying pre-intervention trend	0.99	(0.98, 1.00)	0.99	(0.98, 1.00)	1.00	(0.99, 1.01)
	Level change following intervention	1.82	(1.34, 2.45)	1.83	(1.36, 2.47)	1.35	(0.91, 2.00)
	Slope change following intervention	0.97	(0.95, 0.99)	0.97	(0.95, 0.99)	0.98	(0.96, 1.01)
Sensitivity Analysis #3 - ITS Analysis Stratified by Lockdown Status							
Lockdown Health Facilities							
Outcome	**Parameters**	**Crude Model**		**Adjusted Model***		**Seasonality-Adjusted Model****	
		IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Stillbirth	Underlying pre-intervention trend	0.99	(0.95, 1.03)	0.99	(0.95, 1.03)	1.08	(0.94, 1.24)
	Level change following intervention	1.85	(0.78, 4.38)	1.35	(0.57, 3.17)	0.59	(0.20, 1.69)
	Slope change following intervention	0.98	(0.92, 1.04)	0.98	(0.93, 1.04)	0.81	(0.61, 1.08)
LBW	Underlying pre-intervention trend	1.00	(0.98, 1.02)	1.00	(0.98, 1.02)	0.99	(0.91, 1.07)
	Level change following intervention	1.89	(1.24, 2.90)	1.95	(1.28, 2.99)	1.37	(0.76, 2.47)
	Slope change following intervention	0.95	(0.92, 0.98)	0.95	(0.92, 0.98)	0.96	(0.82, 1.13)
PTB	Underlying pre-intervention trend	0.99	(0.97, 1.01)	0.99	(0.97, 1.01)	1.01	(0.94, 1.09)
	Level change following intervention	1.93	(1.27, 2.91)	2.05	(1.35, 3.10)	1.09	(0.64, 1.86)
	Slope change following intervention	0.96	(0.94, 0.99)	0.96	(0.93, 0.99)	0.91	(0.79, 1.06)
Non-Lockdown Health Facilities							
Outcome	**Parameters**	**Crude Model**		**Adjusted Model***		**Seasonality-Adjusted Model****	

		IRR	95% CI	IRR	95% CI	IRR	95% CI
Stillbirth	Underlying pre-intervention trend	1.01	(0.99, 1.04)	1.02	(0.99, 1.04)	0.99	(0.91, 1.09)
	Level change following intervention	1.04	(0.64, 1.67)	1.06	(0.66, 1.72)	1.42	(0.72, 2.82)
	Slope change following intervention	0.97	(0.93, 1.00)	0.97	(0.93, 1.00)	1.02	(0.85, 1.22)
LBW	Underlying pre-intervention trend	1.02	(1.01, 1.04)	1.02	(1.01, 1.04)	1.06	(1.00, 1.12)
	Level change following intervention	1.03	(0.77, 1.38)	1.02	(0.76, 1.37)	0.71	(0.47, 1.06)
	Slope change following intervention	0.96	(0.94, 0.98)	0.96	(0.94, 0.98)	0.89	(0.80, 0.99)
PTB	Underlying pre-intervention trend	1.00	(0.98, 1.02)	1.01	(0.99, 1.03)	0.96	(0.89, 1.04)
	Level change following intervention	1.46	(0.96, 2.20)	1.51	(1.00, 2.29)	0.89	(0.35, 2.25)
	Slope change following intervention	0.96	(0.94, 0.99)	0.96	(0.93, 0.99)	1.04	(0.90, 1.22)

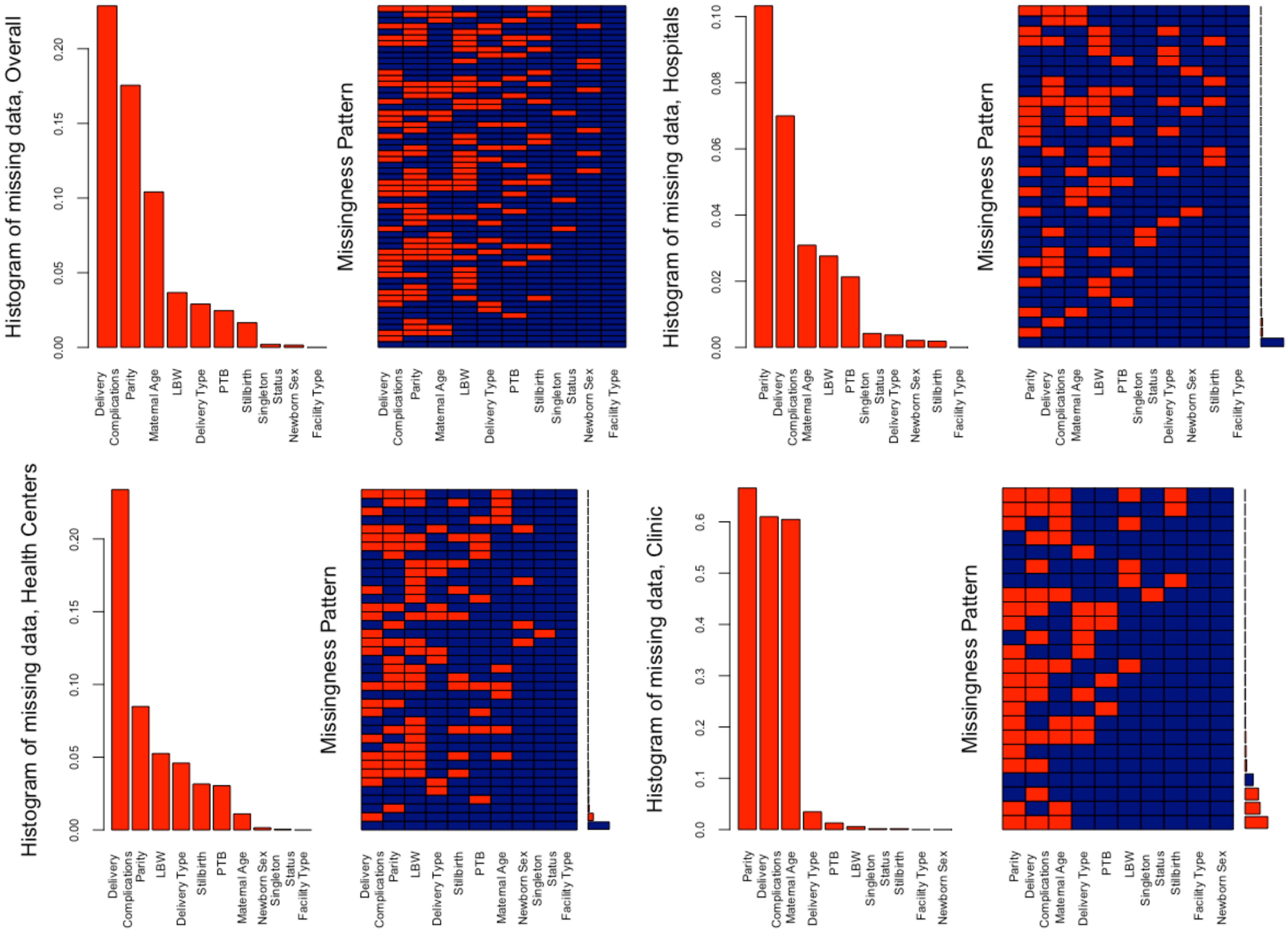
*Crude model + delivery complications and newborn sex. **Adjusted model + Fourier terms accounting for potential seasonality.
CI = confidence interval, IRR = incidence rate ratio, ITS = interrupted time series, LBW = low birth weight, PTB = preterm birth.

Supplemental Figure 3.1. Hypothesized causal diagram depicting variable relationships



ABO = the adverse birth outcomes of interest (i.e., stillbirth, LBW, and PTB), C = observed confounders, Post = dummy variable signifying the time period (i.e., pre-COVID-19 period vs. COVID-19 mitigation period), Treat = the effect of the "treatment" (i.e., the imposition of COVID-19 mitigation measures vs. the absence of such measures), U = unobserved confounders, and Week = time grouped into weekly intervals.

Supplemental Figure 3.2. Missingness patterns, overall and by health-facility type



3.8. References

1. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. *Physiol Genomics*. 2020;52(11):549-557. doi:10.1152/physiolgenomics.00089.2020

2. The Lancet Psychiatry null. COVID-19 and mental health. *Lancet Psychiatry*. 2021;8(2):87. doi:10.1016/S2215-0366(21)00005-5

3. Xiong J, Lipsitz O, Nasri F, et al. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *J Affect Disord*. 2020;277:55-64. doi:10.1016/j.jad.2020.08.001

4. Pierce M, Hope H, Ford T, et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. *Lancet Psychiatry*. 2020;7(10):883-892. doi:10.1016/S2215-0366(20)30308-4

5. Brodeur A, Gray D, Islam A, Bhuiyan S. A literature review of the economics of COVID-19. *J Econ Surv*. 2021;35(4):1007-1044. doi:10.1111/joes.12423

6. Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg Lond Engl*. 2020;78:185-193. doi:10.1016/j.ijsu.2020.04.018

7. Niles MT, Bertmann F, Belarmino EH, Wentworth T, Biehl E, Neff R. The Early Food Insecurity Impacts of COVID-19. *Nutrients*. 2020;12(7):E2096. doi:10.3390/nu12072096

8. Gundersen C, Hake M, Dewey A, Engelhard E. Food Insecurity during COVID-19. *Appl Econ Perspect Policy*. Published online October 2, 2020. doi:10.1002/aepp.13100

9. Gaitán-Rossi P, Vilar-Compte M, Teruel G, Pérez-Escamilla R. Food insecurity measurement and prevalence estimates during the COVID-19 pandemic in a repeated cross-sectional survey in Mexico. *Public Health Nutr*. 2021;24(3):412-421. doi:10.1017/S1368980020004000

10. World Health Organization. Global: WHO Coronavirus (COVID-19) Dashboard. Accessed March 16, 2023. https://covid19.who.int

11. World Health Organization. Democratic Republic of the Congo: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data. Accessed March 16, 2023. https://covid19.who.int

12. World Health Organization. First case of COVID-19 confirmed in the Democratic Republic of the Congo. WHO | Regional Office for Africa. Accessed January 10, 2022. https://www.afro.who.int/news/first-case-covid-19-confirmed-democratic-republic-congo

13. Hategeka C, Carter SE, Chenge FM, et al. Impact of the COVID-19 pandemic and response on the utilisation of health services in public facilities during the first wave in Kinshasa, the

Democratic Republic of the Congo. *BMJ Glob Health*. 2021;6(7):e005955. doi:10.1136/bmjgh-2021-005955

14. Juma CA, Mushabaa NK, Abdu Salam F, Ahmadi A, Lucero-Prisno DE. COVID-19: The Current Situation in the Democratic Republic of Congo. *Am J Trop Med Hyg*. 2020;103(6):2168-2170. doi:10.4269/ajtmh.20-1169

15. Nachega JB, Mbala-Kingebeni P, Otshudiema J, et al. Responding to the Challenge of the Dual COVID-19 and Ebola Epidemics in the Democratic Republic of Congo-Priorities for Achieving Control. *Am J Trop Med Hyg*. 2020;103(2):597-602. doi:10.4269/ajtmh.20-0642

16. Jacobs C, Kyamusugulwa PM, Katembera RS, Kintuntu H. Containing COVID-19 in the Democratic Republic of the Congo: Government Measures and Women's Compliance. *J Afr Law*. 2021;65(S2):287-310. doi:10.1017/S0021855321000371

17. Kashiya Y, Ekofo J, Kabanga C, et al. Multilevel Governance and Control of the COVID-19 Pandemic in the Democratic Republic of Congo: Learning from the Four First Waves. *Int J Environ Res Public Health*. 2023;20(3):1980. doi:10.3390/ijerph20031980

18. Feyissa GT, Tolu LB, Ezeh A. Impact of COVID-19 Pandemic on Sexual and Reproductive Health and Mitigation Measures: The Case of Ethiopia. *Afr J Reprod Health*. 2020;24(s1):24-26. doi:10.29063/ajrh2020/v24i2s.3

19. Govender D, Naidoo S, Taylor M. Don't Let Sexual and Reproductive Health become Collateral Damage in the Face of the COVID-19 Pandemic: A Public Health Perspective. *Afr J Reprod Health*. 2020;24(s1):56-63. doi:10.29063/ajrh2020/v24i2s.9

20. Oyediran KA, Makinde OA, Adelakin O. The Role of Telemedicine in Addressing Access to Sexual and Reproductive Health Services in sub-Saharan Africa during the COVID-19 Pandemic. *Afr J Reprod Health*. 2020;24(s1):49-55. doi:10.29063/ajrh2020/v24i2s.8

21. Siedner MJ, Kraemer JD, Meyer MJ, et al. Access to primary healthcare during lockdown measures for COVID-19 in rural South Africa: an interrupted time series analysis. *BMJ Open*. 2020;10(10):e043763. doi:10.1136/bmjopen-2020-043763

22. Chandir S, Siddiqi DA, Setayesh H, Khan AJ. Impact of COVID-19 lockdown on routine immunisation in Karachi, Pakistan. *Lancet Glob Health*. 2020;8(9):e1118-e1120. doi:10.1016/S2214-109X(20)30290-4

23. KC A, Gurung R, Kinney MV, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. *Lancet Glob Health*. 2020;8(10):e1273-e1281. doi:10.1016/S2214-109X(20)30345-4

24. Shapira G, Ahmed T, Drouard SHP, et al. Disruptions in maternal and child health service utilization during COVID-19: analysis from eight sub-Saharan African countries. *Health Policy Plan*. 2021;36(7):1140-1151. doi:10.1093/heapol/czab064

25. Naqvi S, Naqvi F, Saleem S, et al. Health Care in Pregnancy During the COVID-19 Pandemic and Pregnancy Outcomes in Six Low-and-Middle-Income Countries: Evidence from a Prospective, Observational Registry of the Global Network for Women's and Children's Health. *BJOG Int J Obstet Gynaecol*. Published online April 4, 2022. doi:10.1111/1471-0528.17175

26. Regan AK, Arah O, Fell DB, Sullivan SG. SARS-CoV-2 infection during pregnancy and associated perinatal health outcomes: a national US cohort study. *J Infect Dis*. Published online December 27, 2021:jiab626. doi:10.1093/infdis/jiab626

27. Gurol-Urganci I, Jardine JE, Carroll F, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. *Am J Obstet Gynecol*. 2021;225(5):522.e1-522.e11. doi:10.1016/j.ajog.2021.05.016

28. DeSisto CL, Wallace B, Simeone RM, et al. Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization - United States, March 2020-September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(47):1640-1645. doi:10.15585/mmwr.mm7047e1

29. Stock SJ, Carruthers J, Calvert C, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat Med*. 2022;28(3):504-512. doi:10.1038/s41591-021-01666-2

30. CDC. Pregnant and Recently Pregnant People. Centers for Disease Control and Prevention. Published December 17, 2021. Accessed March 19, 2023. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html

31. Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health*. 2021;9(6):e759-e772. doi:10.1016/S2214-109X(21)00079-6

32. Vaccaro C, Mahmoud F, Aboulatta L, Aloud B, Eltonsy S. The impact of COVID-19 first wave national lockdowns on perinatal outcomes: a rapid review and meta-analysis. *BMC Pregnancy Childbirth*. 2021;21(1):676. doi:10.1186/s12884-021-04156-y

33. Yao XD, Zhu LJ, Yin J, Wen J. Impacts of COVID-19 pandemic on preterm birth: a systematic review and meta-analysis. *Public Health*. 2022;213:127-134. doi:10.1016/j.puhe.2022.10.015

34. Hawco S, Rolnik DL, Woolner A, et al. The impact of mitigation measures on perinatal outcomes during the first nine months of the COVID-19 pandemic: A systematic review with meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2022;274:117-127. doi:10.1016/j.ejogrb.2022.05.007

35. Yang J, D'Souza R, Kharrat A, Fell DB, Snelgrove JW, Shah PS. COVID-19 pandemic and population-level pregnancy and neonatal outcomes in general population: A living systematic review and meta-analysis (Update#2: November 20, 2021). *Acta Obstet Gynecol Scand*. 2022;101(3):273-292. doi:10.1111/aogs.14318

36. Calvert C, Brockway M (Merilee), Zoega H, et al. Changes in preterm birth and stillbirth during COVID-19 lockdowns in 26 countries. *Nat Hum Behav*. Published online February 27, 2023:1-16. doi:10.1038/s41562-023-01522-y

37. Arena PJ, Dzogang C, Gadoth A, et al. Comparison of adverse pregnancy and birth outcomes using archival medical records before and during the first wave of the COVID-19 pandemic in Kinshasa, Democratic Republic of Congo: a facility-based, retrospective cohort study. *BMC Pregnancy Childbirth*. 2023;23(1):31. doi:10.1186/s12884-022-05291-w

38. Gadoth A, Mukadi Nkamba D, Arena PJ, et al. Assessing the feasibility of passive surveillance for maternal immunization safety utilizing archival medical records in Kinshasa, Democratic Republic of the Congo. *Vaccine*. 2022;40(26):3605-3613. doi:10.1016/j.vaccine.2022.04.073

39. Hug L, You D, Blencowe H, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. *The Lancet*. 2021;398(10302):772-785. doi:10.1016/S0140-6736(21)01112-0

40. World Health Organization. Low birth weight. Accessed January 31, 2022. https://www.who.int/data/maternal-newborn-child-adolescent-ageing/advisory-groups/gama/gama-related-resources/nlis

41. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0

42. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol*. 2017;46(1):348-355. doi:10.1093/ije/dyw098

43. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309. doi:10.1046/j.1365-2710.2002.00430.x

44. Zhang F, Wagner AK, Ross-Degnan D. Simulation-based power calculation for designing interrupted time series analyses of health policy interventions. *J Clin Epidemiol*. 2011;64(11):1252-1261. doi:10.1016/j.jclinepi.2011.02.007

45. Li L, Cuerden MS, Liu B, Shariff S, Jain AK, Mazumdar M. Three Statistical Approaches for Assessment of Intervention Effects: A Primer for Practitioners. *Risk Manag Healthc Policy*. 2021;14:757-770. doi:10.2147/RMHP.S275831

46. Craig P, Katikireddi SV, Leyland A, Popham F. Natural Experiments: An Overview of Methods, Approaches, and Contributions to Public Health Intervention Research. *Annu Rev Public Health*. 2017;38:39-56. doi:10.1146/annurev-publhealth-031816-044327

47. DHIS2. In Action. DHIS2. Accessed November 12, 2021. https://dhis2.org/in-action/

48. MEASURE Evaluation. Mapping the Stages of MEASURE Evaluation's Data Use Continuum to DHIS 2: An Example from the Democratic Republic of the Congo — MEASURE Evaluation. Published March 2019. Accessed October 28, 2021. https://www.measureevaluation.org/resources/publications/fs-19-344.html

49. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *Int J Epidemiol*. 2013;42(4):1187-1195. doi:10.1093/ije/dyt092

50. Ramanathan K, Thenmozhi M, George S, et al. Assessing Seasonality Variation with Harmonic Regression: Accommodations for Sharp Peaks. *Int J Environ Res Public Health*. 2020;17(4):1318. doi:10.3390/ijerph17041318

51. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw*. 2011;45:1-67. doi:10.18637/jss.v045.i03

52. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067

53. Goldenberg RL, McClure EM. Have Coronavirus Disease 2019 (COVID-19) Community Lockdowns Reduced Preterm Birth Rates? *Obstet Gynecol*. 2021;137(3):399-402. doi:10.1097/AOG.0000000000004302

54. Cuestas E, Gómez-Flores ME, Charras MD, et al. Association between COVID-19 mandatory lockdown and decreased incidence of preterm births and neonatal mortality. *J Perinatol Off J Calif Perinat Assoc*. 2021;41(10):2566-2569. doi:10.1038/s41372-021-01116-4

55. Caniglia EC, Magosi LE, Zash R, et al. Modest reduction in adverse birth outcomes following the COVID-19 lockdown. *Am J Obstet Gynecol*. 2021;224(6):615.e1-615.e12. doi:10.1016/j.ajog.2020.12.1198

56. Hedermann G, Hedley PL, Bækvad-Hansen M, et al. Danish premature birth rates during the COVID-19 lockdown. *Arch Dis Child Fetal Neonatal Ed*. 2021;106(1):93-95. doi:10.1136/archdischild-2020-319990

57. Hedley PL, Hedermann G, Hagen CM, et al. Preterm birth, stillbirth and early neonatal mortality during the Danish COVID-19 lockdown. *Eur J Pediatr*. 2022;181(3):1175-1184. doi:10.1007/s00431-021-04297-4

58. Simon E, Cottenet J, Mariet AS, et al. Impact of the COVID-19 pandemic on preterm birth and stillbirth: a nationwide, population-based retrospective cohort study. *Am J Obstet Gynecol*. 2021;225(3):347-348. doi:10.1016/j.ajog.2021.05.015

59. Fresson J, Bruckner TA, Ray CL, et al. Decreases in preterm birth during the first COVID-19 lockdown in France by gestational age sub-groups and regional COVID-19 incidence. *Ann Epidemiol*. 2022;72:74-81. doi:10.1016/j.annepidem.2022.05.004

60. Einarsdóttir K, Swift EM, Zoega H. Changes in obstetric interventions and preterm birth during COVID-19: A nationwide study from Iceland. *Acta Obstet Gynecol Scand*. 2021;100(10):1924-1930. doi:10.1111/aogs.14231

61. McDonnell S, McNamee E, Lindow SW, O'Connell MP. The impact of the Covid-19 pandemic on maternity services: A review of maternal and neonatal outcomes before, during and after the pandemic. *Eur J Obstet Gynecol Reprod Biol*. 2020;255:172-176. doi:10.1016/j.ejogrb.2020.10.023

62. Meyer R, Bart Y, Tsur A, et al. A marked decrease in preterm deliveries during the coronavirus disease 2019 pandemic. *Am J Obstet Gynecol*. 2021;224(2):234-237. doi:10.1016/j.ajog.2020.10.017

63. De Curtis M, Villani L, Polo A. Increase of stillbirth and decrease of late preterm infants during the COVID-19 pandemic lockdown. *Arch Dis Child Fetal Neonatal Ed*. 2021;106(4):456. doi:10.1136/archdischild-2020-320682

64. Maeda Y, Nakamura M, Ninomiya H, Ogawa K, Sago H, Miyawaki A. Trends in intensive neonatal care during the COVID-19 outbreak in Japan. *Arch Dis Child Fetal Neonatal Ed*. 2021;106(3):327-329. doi:10.1136/archdischild-2020-320521

65. Kim SY, Kim SY, Kil K, Lee Y. Impact of COVID-19 Mitigation Policy in South Korea on the Reduction of Preterm or Low Birth Weight Birth Rate: A Single Center Experience. *Child Basel Switz*. 2021;8(5):332. doi:10.3390/children8050332

66. Berghella V, Boelig R, Roman A, Burd J, Anderson K. Decreased incidence of preterm birth during coronavirus disease 2019 pandemic. *Am J Obstet Gynecol MFM*. 2020;2(4):100258. doi:10.1016/j.ajogmf.2020.100258

67. Harvey EM, McNeer E, McDonald MF, et al. Association of Preterm Birth Rate With COVID-19 Statewide Stay-at-Home Orders in Tennessee. *JAMA Pediatr*. 2021;175(6):635-637. doi:10.1001/jamapediatrics.2020.6512

68. Kirchengast S, Hartmann B. Pregnancy Outcome during the First COVID 19 Lockdown in Vienna, Austria. *Int J Environ Res Public Health*. 2021;18(7):3782. doi:10.3390/ijerph18073782

69. Simpson AN, Snelgrove JW, Sutradhar R, Everett K, Liu N, Baxter NN. Perinatal Outcomes During the COVID-19 Pandemic in Ontario, Canada. *JAMA Netw Open*. 2021;4(5):e2110104. doi:10.1001/jamanetworkopen.2021.10104

70. Shah PS, Ye XY, Yang J, Campitelli MA. Preterm birth and stillbirth rates during the COVID-19 pandemic: a population-based cohort study. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2021;193(30):E1164-E1172. doi:10.1503/cmaj.210081

71. Li M, Yin H, Jin Z, et al. Impact of Wuhan lockdown on the indications of cesarean delivery and newborn weights during the epidemic period of COVID-19. *PloS One*. 2020;15(8):e0237420. doi:10.1371/journal.pone.0237420

72. Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic. *JAMA*. 2020;324(7):705-706. doi:10.1001/jama.2020.12746

73. Badran EF, Darwish RM, Khader Y, et al. Adverse pregnancy outcomes during the COVID-19 lockdown. A descriptive study. *BMC Pregnancy Childbirth*. 2021;21(1):761. doi:10.1186/s12884-021-04221-6

74. Arnaez J, Ochoa-Sangrador C, Caserío S, et al. Lack of changes in preterm delivery and stillbirths during COVID-19 lockdown in a European region. *Eur J Pediatr*. 2021;180(6):1997-2002. doi:10.1007/s00431-021-03984-6

75. Pasternak B, Neovius M, Söderling J, et al. Preterm Birth and Stillbirth During the COVID-19 Pandemic in Sweden: A Nationwide Cohort Study. *Ann Intern Med*. 2021;174(6):873-875. doi:10.7326/M20-6367

76. Burt JF, Ouma J, Lubyayi L, et al. Indirect effects of COVID-19 on maternal, neonatal, child, sexual and reproductive health services in Kampala, Uganda. *BMJ Glob Health*. 2021;6(8). doi:10.1136/bmjgh-2021-006102

77. Handley SC, Mullin AM, Elovitz MA, et al. Changes in Preterm Birth Phenotypes and Stillbirth at 2 Philadelphia Hospitals During the SARS-CoV-2 Pandemic, March-June 2020. *JAMA*. 2021;325(1):87-89. doi:10.1001/jama.2020.20991

78. Main EK, Chang SC, Carpenter AM, et al. Singleton preterm birth rates for racial and ethnic groups during the coronavirus disease 2019 pandemic in California. *Am J Obstet Gynecol*. 2021;224(2):239-241. doi:10.1016/j.ajog.2020.10.033

79. Wood R, Sinnott C, Goldfarb I, Clapp M, McElrath T, Little S. Preterm Birth During the Coronavirus Disease 2019 (COVID-19) Pandemic in a Large Hospital System in the United States. *Obstet Gynecol*. 2021;137(3):403-404. doi:10.1097/AOG.0000000000004237

80. Dong M, Qian R, Wang J, et al. Associations of COVID-19 lockdown with gestational length and preterm birth in China. *BMC Pregnancy Childbirth*. 2021;21(1):795. doi:10.1186/s12884-021-04268-5

81. Arun Babu T, Sharmila V, Vishnu Bhat B. Curious scenario of changes in incidence of preterm births during COVID-19 pandemic. Pointers for future research? *Eur J Obstet Gynecol Reprod Biol*. 2020;253:333-334. doi:10.1016/j.ejogrb.2020.08.055

82. Sisti G, Joseph JT. Reduction in preterm birth rate during the COVID-19 pandemic: Analysing causation. *BJOG Int J Obstet Gynaecol*. 2023;130(3):285. doi:10.1111/1471-0528.17312

83. Philip RK, Purtill H, Reidy E, et al. Unprecedented reduction in births of very low birthweight (VLBW) and extremely low birthweight (ELBW) infants during the COVID-19 lockdown in Ireland: a "natural experiment" allowing analysis of data from the prior two decades. *BMJ Glob Health*. 2020;5(9):e003075. doi:10.1136/bmjgh-2020-003075

84. Maki Y, Tokuda A, Kino E, Yamauchi A, Ohtsuka T, Terao K. No significant changes in preterm birth, low-birth-weight, and small-for-gestational-age infants during the first year of the COVID-19 pandemic in a rural area in Japan. *J Obstet Gynaecol Res*. 2023;49(1):175-181. doi:10.1111/jog.15446

85. Ditekemena JD, Nkamba DM, Muhindo HM, et al. Factors associated with adherence to COVID-19 prevention measures in the Democratic Republic of the Congo (DRC): results of an online survey. *BMJ Open*. 2021;11(1):e043356. doi:10.1136/bmjopen-2020-043356

86. Akilimali PZ, Mashinda DK, Lulebo AM, Mafuta EM, Onyamboko MA, Tran NT. The emergence of COVID-19 in the Democratic Republic of Congo: Community knowledge, attitudes, and practices in Kinshasa. *PloS One*. 2022;17(6):e0265538. doi:10.1371/journal.pone.0265538

87. Nkamba DM, Arena PJ, Gadoth A, et al. Adherence to face mask use during the COVID-19 pandemic among women seeking antenatal care in Kinshasa, Democratic Republic of Congo: a facility-based cross-sectional study. *BMJ Open*. 2022;12(7):e060929. doi:10.1136/bmjopen-2022-060929

88. Basu S, Meghani A, Siddiqi A. Evaluating the Health Impact of Large-Scale Public Policy Changes: Classical and Novel Approaches. *Annu Rev Public Health*. 2017;38:351-370. doi:10.1146/annurev-publhealth-031816-044208

89. Dimick JB, Ryan AM. Methods for evaluating changes in health care policy: the difference-in-differences approach. *JAMA*. 2014;312(22):2401-2402. doi:10.1001/jama.2014.16153

90. Kogan NE, Gantt S, Swerdlow D, et al. Leveraging Serosurveillance and Postmortem Surveillance to Quantify the Impact of Coronavirus Disease 2019 in Africa. *Clin Infect Dis*. 2023;76(3):424-432. doi:10.1093/cid/ciac797

91. Nkuba AN, Makiala SM, Guichet E, et al. High Prevalence of Anti–Severe Acute Respiratory Syndrome Coronavirus 2 (Anti–SARS-CoV-2) Antibodies After the First Wave of Coronavirus Disease 2019 (COVID-19) in Kinshasa, Democratic Republic of the Congo: Results of a Cross-sectional Household-Based Survey. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021;74(5):882-890. doi:10.1093/cid/ciab515

92. Arie S. Congo sees rise in deaths from malaria, measles, and cholera as Ebola outbreak swallows up resources. *BMJ*. 2019;366:l4522. doi:10.1136/bmj.l4522

93. Nachega JB, Mbala-Kingebeni P, Otshudiema J, Zumla A, Tam-Fum JJM. The colliding epidemics of COVID-19, Ebola, and measles in the Democratic Republic of the Congo. *Lancet Glob Health*. 2020;8(8):e991-e992. doi:10.1016/S2214-109X(20)30281-3

94. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ*. 2015;350:h2750. doi:10.1136/bmj.h2750

95. Penfold RB, Zhang F. Use of Interrupted Time Series Analysis in Evaluating Health Care Quality Improvements. *Acad Pediatr*. 2013;13(6):S38-S44. doi:10.1016/j.acap.2013.08.002

96. McCleary L. Using multiple imputation for analysis of incomplete data in clinical research. *Nurs Res*. 2002;51(5):339-343. doi:10.1097/00006199-200209000-00012

97. Nissen F, Quint JK, Morales DR, Douglas IJ. How to validate a diagnosis recorded in electronic health records. *Breathe Sheff Engl*. 2019;15(1):64-68. doi:10.1183/20734735.0344-2018

98. Beaulieu-Jones BK, Lavage DR, Snyder JW, Moore JH, Pendergrass SA, Bauer CR. Characterizing and Managing Missing Structured Data in Electronic Health Records: Data Analysis. *JMIR Med Inform*. 2018;6(1):e8960. doi:10.2196/medinform.8960

Chapter 4. The Impact of COVID-19 Mitigation Measures on Neonatal Health Outcomes in sub-Saharan Africa: A Systematic Review and Meta-Analysis

4.1. Abstract

Conflicting results exist regarding the impact of COVID-19 policies on neonatal health outcomes; moreover, associated investigations within sub-Saharan Africa have been limited. In response, this systematic review and meta-analysis was performed to assess the relationship between COVID-19 mitigation measures and stillbirth, low birth weight (LBW), and preterm birth (PTB) in sub-Saharan Africa. We searched six databases from January 2020 to December 2022 using applicable keywords and performed abstract/full article screening to produce a list of final studies. These studies were assessed for their risk of bias and described via narrative synthesis. Meta-analysis with random effects was performed to generate overall risk ratios (RRs) as well as RRs stratified by study design with 95% confidence intervals (CIs). The study protocol was registered with PROSPERO (CRD42022335390). Our search identified 515 unique studies, of which sixteen were included. Studies were identified across twelve countries; seven were multi-/single-center examinations, six were multi-national/national/regional investigations, and three were survey studies. Additionally, most studies were categorized as being at moderate risk of bias ($n = 10$). For stillbirth, the overall RR indicated an increase during COVID-19 mitigation measures (RR: 1.17; 95% CI: 1.04, 1.32); however, among multi-national/national/regional studies, there was no increase (RR: 1.03; 95% CI: 0.97, 1.09). Similarly, the overall LBW RR suggested an increase during COVID-19 mitigation measures (RR: 1.18; 95% CI: 0.90, 1.56); however, among multi-national/national/regional studies, there was no increase (RR: 0.97; 95% CI: 0.91, 1.04). For PTB, the overall RR indicated no increase during COVID-19 mitigation measures (RR: 1.00; 95% CI: 0.94, 1.07); no differences were detected when stratified by study design. We hope that our

findings provide insights for African health officials regarding the real-world effects of COVID-19 mitigation measures and spur continued research in this subject so that a more complete picture of the sub-Saharan African experience can be formed.

4.2. Introduction

As has already been discussed, there is yet to be a global consensus on the association between COVID-19 mitigation measures and adverse birth outcomes as a variety of observational investigations have provided conflicting results.[1–5] Although some studies have demonstrated that pregnant women and their newborns in low- and middle-income countries (LMICs) may be more vulnerable to certain adverse health outcomes compared to their counterparts in high-income countries (HICs) as a result of the COVID-19 pandemic,[1,6,7] our understanding of the situation in sub-Saharan Africa remains extremely limited. For example, a recent systematic review and meta-analysis on the association between COVID-19 mitigation measures and perinatal outcomes during the first nine months of the pandemic identified 38 studies that examined stillbirth, low birth weight (LBW), preterm birth (PTB), and neonatal intensive care admission from the start of the pandemic until May 2021;[4] however, only one of these studies (i.e., Caniglia et al.)[8] was conducted in a sub-Saharan African country (i.e., Botswana). Similarly, a living systematic review and meta-analysis on the association between the COVID-19 pandemic and pregnancy/neonatal outcomes identified over 50 studies that analyzed stillbirth, LBW, PTB, neonatal mortality, and maternal mortality,[5] yet only three of these studies (i.e., Caniglia et al.,[8] Kassie et al.,[9] and Shakespeare et al.[10]) were conducted in sub-Saharan African countries (i.e., Botswana, Ethiopia, and Zimbabwe, respectively).

This dearth of data for sub-Saharan African countries represents a gap in the literature that needs to be filled for a variety of reasons. First, the COVID-19 experience in sub-Saharan Africa has been substantially different compared to other regions of the world. For example, the World Health Organization (WHO) African Region has recorded only 9.5 million confirmed cases of COVID-19 and 175,315 COVID-19 deaths as of March 6, 2023;[11] the United States (US) alone, on the other hand, has recorded about 102.4 million confirmed cases of COVID-19 (i.e., nearly eleven times as many confirmed cases) and about 1.1 million COVID-19 deaths (i.e., slightly more than six times as many deaths) over the same time period.[12] Although differences in population structures, testing capabilities, laboratory infrastructure, and healthcare workforce development may all contribute to the wide gulf in reported case numbers and deaths between the US and the WHO African Region,[13,14] sub-Saharan Africa still never experienced the deluge of cases and deaths predicted by initial models and forecasts.[15–17] Additionally, due to the fact that many of the countries in sub-Saharan Africa have had recent and/or continuous encounters with other infectious disease outbreaks, most of them quickly adopted comprehensive mitigation measures in their initial responses to the COVID-19 pandemic.[18] Thus, a targeted examination of the impact of COVID-19 mitigation measures on adverse birth outcomes in sub-Saharan Africa would provide an opportunity to better understand the impact of such rapidly deployed pandemic policies in a region of the world that has experienced relatively low numbers of (symptomatic) COVID-19 cases.

Furthermore, the populations that have provided the majority of information about the association between COVID-19 mitigation measures and adverse birth outcomes differ significantly from the general populations found throughout sub-Saharan Africa.[19–21] For instance, sub-Saharan Africa is an overall younger region when compared to the rest of the world. More specifically, the demographic age structures for Europe, the Americas, and Asia have median ages ranging from 32 to 42.5 years with 8.9% to 19.1% of the population aged greater than 65 years;

conversely, the median age in sub-Saharan Africa is 18 years with only 3.0% of the population aged greater than 65 years.[19] Somewhat similarly, the prevalence and incidence of other infectious diseases (e.g., HIV/AIDS, malaria, and tuberculosis) is higher in sub-Saharan Africa compared to other regions of the world; for example, the WHO African Region accounted for almost two-thirds of the global total of new HIV infections in 2018.[22] More importantly though, the burden of adverse birth outcomes is much higher in sub-Saharan Africa than in other regions of the world. For instance, a systematic assessment of global stillbirths from 2000 to 2019 concluded that sub-Saharan Africa had the highest stillbirth rates in 2019.[23] Likewise, a 2014 systematic review of PTB estimates concluded that sub-Saharan Africa had the second highest PTB rate in the world (behind North Africa);[24] moreover, a 2015 systematic analysis found that sub-Saharan Africa also had the second highest LBW rate in the world (behind Southern Asia).[25] Therefore, sub-Saharan Africa provides a suitable context to detect small decreases and/or increases in adverse birth outcome rates that might not have been possible to detect elsewhere due to the high incidence of these outcomes there.

Lastly, this knowledge gap needs to be addressed to assure global health parity.[26] Even though the COVID-19 pandemic has had less of a direct impact in sub-Saharan Africa compared to North America or Europe in terms of reported case numbers, the unique situation in sub-Saharan Africa still warrants further investigation in order to provide critical health information for the region and also further the global dialogue in this area of research. Therefore, this study served to address this critical research gap by performing a systematic review and meta-analysis on the relationship between COVID-19 mitigation measures and selected adverse birth outcomes (i.e., stillbirth, LBW, and PTB) among pregnant women and their newborns in sub-Saharan Africa in order to provide a centralized source of information on this subject.

4.3. Methods

Population, intervention, comparator, and outcome (PICO)

As this systematic review and meta-analysis focused on the context of sub-Saharan Africa, the studies were limited to only include investigations among pregnant women and their newborns that occurred in sub-Saharan African countries. We used the regional grouping scheme of the African Union (AU) to define sub-Saharan Africa;[27] therefore, sub-Saharan Africa encompassed all the AU member states that are not part of the Northern Africa geographic region in this study. More specifically, we defined sub-Saharan Africa as all the member states of the AU except for Algeria, Egypt, Libya, Mauritania, Morocco, Sahrawi Republic/Western Sahara, and Tunisia, thereby resulting in forty-eight total countries as part of sub-Saharan Africa for this systematic review and meta-analysis. Additionally, the intervention of interest was COVID-19 mitigation measures. As COVID-19 outbreak responses were highly variable throughout sub-Saharan Africa,[18] we used the Oxford Coronavirus Government Response Tracker project's national stringency index, which is a composite measure of nine response metrics (i.e., school closures, workplace closures, cancellation of public events, restrictions on public gatherings, closures of public transport, stay-at-home requirements, public information campaigns, restrictions on internal movements, and international travel controls), to quantify the strength of the COVID-19 mitigations measures across the intervention period;[28,29] the stringency index was calculated as the mean score (and range) of the nine metrics across the intervention period at the national level and ranged from 0 (i.e., no response) to 100 (i.e., strictest response possible).[28,29]

Furthermore, the treated group comprised of the pregnant women and their newborns that had their index delivery in the intervention period (i.e., during COVID-19 mitigation measures). The control group, on the other hand, comprised of the pregnant women and their newborns that had their index delivery in either one of two periods: 1) the months/weeks immediately prior to the imposition of COVID-19 mitigation measures or 2) the equivalent months/weeks of the COVID-19 mitigation measures period but during previous years (i.e., during a historical control period). Moreover, there were three primary outcomes of interest that were defined per standard practices: stillbirth, LBW, and PTB. More specifically, stillbirth was defined as the birth of a baby following fetal death either before or during labor or birth,[23] LBW was defined as a newborn with a birth weight less than 2,500 grams,[30] and PTB was defined as a birth before 37 completed weeks of gestation or fewer than 259 days from the first date of a woman's last menstrual period.[24]

Search strategy and inclusion/exclusion criteria

We performed searches in the following six databases from January 1, 2020 through December 31, 2022: PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, Web of Sciences, African Journals Online (AJOL), African Index Medicus (AIM), and the WHO COVID-19 Database. We tailored our combination of subject headings/controlled vocabulary/thesauri (e.g., Medical Subject Headings in PubMed/MEDLINE) along with regular keyword fields (e.g., title and abstract) for each database in order to establish a comprehensive search strategy. The overall search strategy was formulated according to the PICO model;[31,32] the search string combinations used for each database along with their corresponding PICO components are provided in Supplemental Tables 4.1 through 4.6. Zotero[33] was used to save and organize references, identify duplicates between different databases, and provide an interface for screening. Additionally, it should be noted that no language restrictions were applied since a wide variety of languages (e.g., English, French, and Portuguese) are spoken throughout sub-Saharan Africa.

Moreover, studies that directly compared pregnant women with and without diagnosed COVID-19/severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, investigations that did not explicitly include a comparator period/population, and/or analyses conducted in a country outside of sub-Saharan Africa (as previously defined) were excluded from the final list of included studies. We also excluded cross-country comparisons, case reports, case series, simulation/modelling-based analyses, animal studies, and editorials/commentaries because these study types were not able to meaningfully contribute to our analyses and/or interpretations. Furthermore, it should be emphasized that only observational studies were included for this systematic review and meta-analysis. Lastly, results from Chapter 3: The Impact of COVID-19 Mitigation Measures on Neonatal Health Outcomes in Kinshasa, Democratic Republic of the Congo: An Interrupted Time Series Analysis[34] were also incorporated into this systematic review and meta-analysis.

Data extraction and bias assessments

After searching the databases and importing the relevant results, we first performed abstract screening (in collaboration with an external researcher, Jane Bandak to ensure objectivity in the data extraction process) to select for studies reporting on maternal and neonatal health outcomes before and during the pandemic; after this initial screening round, full text screening was performed to select for studies that explicitly investigated stillbirth, LBW, and/or PTB. Discrepancies were resolved through consensus discussion between the two reviewers. After a list of studies was generated from this review process, the reference list of each included study was also examined to identify any additional studies. Data elements were extracted from the selected studies using a standardized form;[35] the following items were extracted via the standardized form: first author, journal name, country, World Bank economic classification,[36] AU regional group, data type, specific city/region, urbanicity, control study period, treated study period, type of control period, study design, average maternal age, singleton pregnancies, confounder control, seasonality control, Oxford COVID-19 Government Response Tracker stringency score (mean and range), stillbirth details (e.g., definition, effect estimate, and sample size), LBW details (e.g., definition, effect estimate, and sample size), and PTB details (e.g., definition, effect estimate, and sample size) (Supplemental Figure 4.1). Lastly, in the situation that a potential study was determined to lack any necessary details, the corresponding study author was contacted to obtain the required information.

All included studies were also assessed for their quality/risk of bias. Since this systematic review and meta-analysis only included observational studies, the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used to assess study quality; thus, risk of bias was first assessed across the seven domains of the ROBINS-I tool (i.e., confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result), and then studies were ultimately categorized as being at either low, moderate, serious, or critical risk of bias per the recommendations of the ROBINS-I authors.[37] Each study was assessed by the two reviewers and discrepancies were resolved through consensus discussion. Additionally, funnel plots were used to visually examine for the presence of publication bias (i.e., "the tendency for authors to submit, and of journals to accept, manuscripts for publication based on the direction or strength of the study findings" that therefore leads to an overabundance of statistically significant results relative to null findings)[38,39] when ten or more studies were available for a given outcome. Formal statistical tests (i.e., Begg's test and Egger's test)[40] were also used to statistically test for publication bias when ten or more studies were available for a given outcome.

Data synthesis and analyses

A narrative synthesis of the details from the included studies was first performed; in support of this narrative synthesis, a table of key extracted data elements from each study was produced. Furthermore, results from each study were graphically displayed together along with their corresponding 95% confidence intervals (CIs) in the form of a forest plot. Additionally, heterogeneity in the study results was expected due to sampling error and natural variation in effect; however, other sources of heterogeneity (e.g., variation due to economic status) were also expected, and thus statistical tests for heterogeneity were performed.[35] More specifically, the Higgins I^2 test statistic was employed to determine the proportion of total variation across the studies that was due to between-study heterogeneity; an I^2 value less than 25% was considered indicative of "low" heterogeneity, an I^2 value between 25% and 75% was considered indicative of "moderate" heterogeneity, and an I^2 value greater than 75% was considered indicative of "high" heterogeneity.[41]

For the quantitative synthesis, we employed separate meta-analyses with a random-effects approach in order to generate overall risk ratios (RRs) with corresponding 95% CIs examining the impact of COVID-19 mitigation measures on each of stillbirth, LBW, and PTB according to the DerSimonian and Laird method.[42] We thus assumed that the true effect size varied from study to study, thereby producing more conservative estimates that have wider CIs but that are also not as influenced by larger studies (as a result of the random-effects approach).[43] However, as suggested by Egger and Smith,[35] the robustness of our findings was also examined through a sensitivity analysis that employed a fixed-effects approach as opposed to a random-effects approach. Additionally, only studies that evaluated stillbirth, LBW, or PTB at the individual level were used to generate the overall RRs (in order to ensure that only similar types of studies were combined);

thus, any studies that employed interrupted time series (ITS) analyses at the aggregated level were not included unless it was possible to derive individual-level results (based on either the data presented in the article or data provided by the corresponding author upon request). Moreover, when studies presented adjusted results, these estimates were used in place of crude results, thereby requiring utilization of the inverse variance method to generate our overall RRs.

Furthermore, the primary subgroup analysis focused on how the impact of COVID-19 mitigation measures varied depending on the study design, as other analyses in this area have demonstrated that results can potentially differ depending on whether national/regional or multi-/single-center data are used;[5,7] thus, subgroup meta-analyses with a random-effects approach, in which the studies were stratified by study design (i.e., multi-national/national/regional, multi-/single-center, or survey study), were performed to generate stratified RRs with corresponding 95% CIs. Other pre-planned subgroup meta-analyses were performed based on the following (stratification) variables of interest: World Bank economic classification (i.e., low- or middle-income), AU regional grouping (i.e., Central, Eastern, Western, or Southern Africa), type of control period (i.e., immediately prior to the imposition of mitigation measures or during a historical control period), and national mitigation measures stringency (as determined by the mean Oxford COVID-19 Government Response Tracker stringency score). Lastly, all statistical analyses were conducted using the *meta* package[44] within R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval and other considerations

This systematic review and meta-analysis did not require institutional review board approval as the data that informed the research were publicly available and collected from existing online databases; additionally, this research did not involve any human subjects so informed consent was not required. Furthermore, the associated protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022335390) to assure accountability and counter publication bias.[45] Lastly, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions were followed here to ensure clarity and transparency in our results.[46]

4.4. Results

General characteristics

We ultimately found a total of sixteen applicable studies for this systematic review and meta-analysis. Of the 515 unique records initially identified, 420 were excluded after abstract review; most records were excluded because they evaluated the direct effect of SARS-CoV-2 infection/COVID-19 diagnosis on birth outcomes (n = 114) or they did not explicitly include a comparator period (n = 88). A further 79 articles were excluded after full-text screen; the primary reason that these articles were excluded was that they evaluated a neonatal health outcome other than stillbirth, LBW, or PTB (n = 34). Additionally, one article was excluded during the data extraction process due to the fact that it briefly discussed the impact of the COVID-19 pandemic on stillbirth but did not provide any direct data on the association; the corresponding author was contacted, but we were still not able to acquire the necessary information, so the article was ultimately excluded. Furthermore, the individual-level results (adjusted for the same confounders as was the case for the associated ITS analysis) from Chapter 3 were incorporated, thereby resulting in sixteen final studies for inclusion (Figure 4.1).

Populations that informed these sixteen studies came from the following countries: Botswana (n = 1), Democratic Republic of the Congo (DRC, n = 2), Ethiopia (n = 3), Ghana (n =

1), Kenya (*n* = 2), Malawi (*n* = 1), Mozambique (*n* = 1), Nigeria (*n* = 2), South Africa (*n* = 1), Uganda (*n* = 1), Zambia (*n* = 1), and Zimbabwe (*n* = 3); thus, studies were identified across twelve total sub-Saharan African countries (Figure 4.2). Five of these countries were classified as low-income (41.67%), an additional five were classified as lower middle-income (41.67%), and the remaining two countries were classified as upper middle-income (16.67%); therefore, slightly more than half of the identified countries were middle-income countries (58.33%). At the study level, nearly half were multi-/single-center investigations (*n* = 7, 43.75%), while the remainder were either multi-national/national/regional studies (*n* = 6, 37.50%) or survey studies (*n* = 3, 18.75%). Mean Oxford COVID-19 Government Response Tracker stringency score ranged from 53.8 to 84.1 across the included studies; investigations with lower Oxford COVID-19 Government Response Tracker stringency scores often analyzed extended COVID-19 mitigation measures periods that included both lockdown and non-lockdown periods, while studies with higher Oxford COVID-19 Government Response Tracker stringency scores were ones that primarily focused only on periods when lockdown measures were in place. The majority of the studies (*n* = 12) evaluated stillbirth, while a much smaller number analyzed either LBW (*n* = 5) or PTB (*n* = 6); moreover, only two studies examined all three outcomes simultaneously (Table 4.1).

Additionally, most studies were categorized as being at moderate risk of bis (*n* = 10); only two studies were considered to be at low risk of bias, while the remaining four studies were determined to be at serious (*n* = 3) or critical (*n* = 1) risk of bias. Concerns regarding bias due to confounding as well as bias in the measurement of outcomes were the primary reasons studies were considered to be at moderate to critical risk of bias; a large number of studies also did not provide information regarding potential bias due to missing data, so we were not able to provide consistent judgement regarding this domain (Supplemental Figure 4.2). Lastly, it should be noted that individual-level data were not able to be extracted from Lydon et al.[47] as they performed an ITS at the aggregated level in their primary analyses; thus, this study was not included in any of the quantitative syntheses. Furthermore, Chimhuya et al.[48] conducted two separate analyses (i.e., one analysis within Malawi and another analysis within Zimbabwe), so the corresponding results were kept separate throughout the quantitative syntheses.

Stillbirth

A total of eleven studies comprising of 506,286 deliveries occurring during COVID-19 mitigation measures and 525,629 deliveries occurring during the pre-pandemic period (i.e., 1,031,915 total deliveries) were included for the random-effects meta-analysis of stillbirth. The overall RR indicated that there was a statistically significant increase in the risk of stillbirth during the COVID-19 mitigation measures period (RR: 1.17; 95% CI: 1.04, 1.32); however, the I^2 was 91.5%, thereby indicating a high amount of heterogeneity in the results. When stratified by study design, we found there was still a statistically significant increase in the risk of stillbirth during the imposition of COVID-19 mitigation measures (RR: 1.37; 95% CI: 1.15, 1.63) as well as high heterogeneity (I^2 = 85.8%) among the studies that employed a multi-/single-center design; however, among the studies that employed a multi-national/national/regional study design, we found that there was no increase in the risk of stillbirth during the imposition of COVID-19 mitigation measures (RR: 1.03; 95% CI: 0.97, 1.09) and only moderate heterogeneity (I^2 = 34.1%). For studies that utilized a survey design, the results suggested a potential increase in the risk of stillbirth (RR: 1.52; 95% CI: 0.80, 2.88; I^2 = 47.3%), but only two studies were categorized as surveys (so therefore these results should be interpreted with caution) (Figure 4.3). Visual inspection of the stillbirth funnel plot suggested a low to moderate risk of publication bias; however, the lower portion of the funnel plot was virtually empty, thereby indicating that some smaller studies were potentially missing (Supplemental Figure 4.3). Nonetheless, the corresponding Egger's ($p = 0.2436$) and Begg's ($p = 0.6971$) tests also revealed that there was no evidence of publication bias for stillbirth.

LBW

For the random-effects meta-analysis of LBW, a total of five studies (that contributed six different study populations) comprising of 40,488 deliveries occurring during COVID-19 mitigation measures and 38,778 deliveries occurring during the pre-pandemic period (i.e., 79,276 total deliveries) were included. The overall RR suggested that there was a potential increase in the risk of LBW during the COVID-19 mitigation measures period (RR: 1.18; 95% CI: 0.90, 1.56); however, the I^2 was 98.4%, thereby indicating a high amount of heterogeneity in the results. When stratified by study design, we found that the results still suggested that there was still an increase in the risk of LBW during the imposition of COVID-19 mitigation measures (RR: 1.30; 95% CI: 0.90, 1.90) as well as high heterogeneity ($I^2 = 98.8\%$) among the studies that employed a multi-/single-center design. However, among the studies that employed a multi-national/national/regional study design, we found that there was no increase in the risk of LBW during the imposition of COVID-19 mitigation measures (RR: 0.97; 95% CI: 0.91, 1.04) and low heterogeneity ($I^2 = 0.0\%$); still, it should be highlighted that only two studies were categorized as multi-national/national/regional, so therefore these results should be interpreted with caution (Figure 4.4). Furthermore, publication bias was not assessed for LBW due to the fact that less than ten studies were included for this outcome.

PTB

Regarding the random-effects meta-analysis of PTB, a total of six studies (that contributed seven different study populations) comprising of 33,154 deliveries occurring during COVID-19 mitigation measures and 49,834 deliveries occurring during the pre-pandemic period (i.e., 82,988 total deliveries) were included. The overall RR indicated that there was no increase in the risk of PTB during the COVID-19 mitigation measures period (RR: 1.00; 95% CI: 0.94, 1.07); additionally, the I^2 was 62.4%, thereby indicating a moderate amount of heterogeneity in the results. When stratified by study design, results were mostly consistent. For example, no increase in the risk of PTB during the imposition of COVID-19 mitigation measures was found among either multi-national/national/regional studies (RR: 0.97; 95% CI: 0.90, 1.06) or investigations that utilized a multi-/single-center design (RR: 1.03; 95% CI: 0.94, 1.14) (Figure 4.5). Furthermore, publication bias was not assessed for PTB due to the fact that less than ten studies were included for this outcome.

Additional analyses

When modifying the meta-analysis to use a fixed-effects as opposed to a random-effects approach, the overall RRs for each outcome were largely unchanged. For instance, the fixed-effects estimate for stillbirth (RR: 1.11; 95% CI: 1.08, 1.14) and PTB (RR: 1.00; 95% CI: 0.96, 1.03) still indicated a statistically significant increase and the lack of any change during the COVID-19 mitigation measures period, respectively. However, for LBW, the fixed-effects estimate represented a statistically significant result (RR: 1.20; 95% CI: 1.16, 1.24), a finding that was in contrast with the random-effects estimate (RR: 1.18; 95% CI: 0.90, 1.56) (data not shown). Regarding the other pre-planned subgroup meta-analyses (i.e., by World Bank economic classification, AU regional grouping, type of control period, and national mitigation measures stringency), additional sources of heterogeneity were ultimately not identified across the three outcomes. For example, when stratified by World Bank economic classification, the risk of stillbirth during the COVID-19 mitigation measures was similar between low-income (RR: 1.21;

95% CI: 0.99, 1.48) and middle-income countries (RR: 1.15; 95% CI: 0.95, 1.40); similarly, when stratified by type of control period, the risk of PTB during COVID-19 mitigation measures was similar between studies that used a historical control period (RR: 1.02; 95% CI: 0.95, 1.10) and studies that used a control period immediately before the imposition of pandemic policies (RR: 0.97; 95% CI: 0.84, 1.11) (data not shown).

4.5. Discussion

Summary

This systematic review and meta-analysis evaluated the impact of COVID-19 mitigation measures on three key adverse birth outcomes (i.e., stillbirth, LBW, and PTB) in sub-Saharan Africa; our results generally suggested that the risk of stillbirth and LBW potentially increased during the imposition of COVID-19 mitigation measures while the risk of PTB did not change during such periods. However, there were significant differences for stillbirth and LBW between studies that utilized multi-national/national/regional data and investigations that employed multi-/single-center designs as multi-national/national/regional studies indicated there was no change in the risk of either outcome during COVID-19 mitigation measures. Despite issues associated with high levels of heterogeneity for certain outcomes, our results still provide key insights into how the COVID-19 pandemic affected neonatal health in sub-Saharan Africa; additionally, this investigation helped to highlight the need for further research in this topic area as we were only able to identify studies in a relatively small number of sub-Saharan African countries.

Literature comparisons

As previously mentioned, there has yet to be a global consensus on the association between COVID-19 policies and perinatal health outcomes due to inconsistent results from a variety of studies, thereby making it challenging to draw broad conclusions or generalize findings across populations. Indeed, other meta-analyses and large-scale studies in this area have also produced somewhat conflicting results.[1–7] For example, meta-analyses by Chmielewska et al.[1] and Vaccaro et al.[2] reported increases in stillbirth during the pandemic period (a finding in line with our overall results), while meta-analyses by Yang et al.[5] and Hawco et al.[4] reported no change in the stillbirth rate during the pandemic period. Moreover, a large-scale ITS and meta-analysis using data from approximately 52 million births across 26 countries reported slightly conflicting results for stillbirth among HICs but also reported an increase in the risk of stillbirth in Brazil.[7] Somewhat similarly, Chmielewska et al.[1] and Hawco et al.[4] reported no change in LBW during the pandemic period, while Vaccaro et al.[2] and Yang et al.[5] reported a decrease and an increase (as was suggested by our overall results) in LBW during the pandemic period, respectively. Likewise, Chmielewska et al.,[1] Hawco et al.,[4] and Yang et al.[5] identified no change in PTB during the pandemic period (thereby agreeing with our overall results), while Vaccaro et al.,[2] Yao et al.,[3] and Calvert et al.[7] documented decreases in PTB during the pandemic period.

Nonetheless, direct comparisons to other meta-analyses on this topic area are challenging due to the fact that these investigations mostly included studies that were conducted in HICs; in fact, a few of these analyses even highlighted the lack of data from LMICs (including ones in sub-Saharan Africa) as limitations to their generalizability.[2,5,7] Another complication relates to the fact that other meta-analyses have investigated the association between the COVID-19 pandemic and neonatal outcomes from a variety of perspectives; for instance, Hawco et al.[4] took a targeted approach and investigated the impact of "mitigation measures on perinatal outcomes during the first nine months of the COVID-19 pandemic," while Yang et al.[5] and Yao et al.[3] investigated the impact of the COVID-19 pandemic more generally (i.e., they did not necessarily focus on specific mitigation measures, like lockdowns). Additionally, our systematic review and meta-analysis identified a relatively lower number of studies for inclusion; for example, Yao et al.[3] included 63 studies after their study identification and screening process, thereby obtaining a final number much higher than the sixteen studies selected here. Therefore, we ultimately recommend caution when comparing our findings to other meta-analyses in this topic area.

Study design differences and other considerations

Though our overall RRs suggested increases in the risk of stillbirth and LBW during the COVID-19 mitigation measures period compared to the pre-pandemic period, there were high levels of heterogeneity for these outcomes as indicated by the Higgins I^2. Since there is a risk that meta-analyses may produce spurious results when heterogeneity is high, it is generally recommended that a "thorough consideration of possible sources of heterogeneity between observational studies should be given more weight than an overall measure of effect as such an approach can provide more important insights;"[49] it should thus be emphasized here how the stratified RRs differed by study design. More specifically, multi-national/national/regional studies indicated that there was no change in the risk of stillbirth or LBW during COVID-19 mitigation measures (and that these results did not suffer from increased heterogeneity), while multi-/single-center investigations indicated that there was an increase in the risk of stillbirth or LBW during COVID-19 mitigation measures. As suggested by Yang et al.[5] though, differences in findings between multi-/single-center studies and multi-national/national/regional investigations could reflect changes in referral patterns due to reduced access as a result of the pandemic; other explanations could relate to (high-risk) pregnant women potentially opting to give birth in areas with a lower COVID-19 prevalence or in hospitals that were not treating COVID-19 patients.[50] Similarly, Calvert et al.[7] discuss how such differences may relate to facility-specific challenges in the reporting of key variables and/or facility-specific shifts in pregnancy care, thereby leading them to urge "caution in the interpretation of results" from multi-/single-center studies.[7]

As was the case when comparing our results to other meta-analyses, another aspect to consider here related to the fact that the studies included in our systematic review and meta-analysis investigated the association between the COVID-19 pandemic and neonatal outcomes from differing perspectives. For example, Ezenwa et al.[51] focused exclusively on the lockdown period, which lasted only three months, while Naqvi et al.[52] examined a more general COVID-19 period that lasted twelve months and thus included lockdown and non-lockdown periods. Though we used the Oxford Coronavirus Government Response Tracker to help account for these differences in the strength of the mitigation measures, it may be the case that these differing approaches hindered our ability to validly combine our included studies via quantitative synthesis. Furthermore, only five studies (that contributed six different study populations) and six studies (that contributed seven different study populations) were included for LBW and PTB, respectively; thus, we urge caution in the interpretation of these results, especially for LBW as only two such studies were categorized as multi-national/national/regional. Lastly, only three studies in this systematic review and meta-analysis were categorized as surveys, so it was not possible to make definitive conclusions on how such studies differed from multi-national/national/regional investigations and multi-/single-center studies; in general though, the survey studies had issues concerning bias in the measurement of outcomes (due to the potential for recall bias) and thus were considered to be at a higher risk of bias than the other study design types.

Public health and research implications

Despite these caveats regarding the interpretation of our results, this systematic review and meta-analysis still served to provide more context on how COVID-19 pandemic policies affected neonatal health outcomes in sub-Saharan Africa. As most of the available literature in this area has come from HICs and countries outside of sub-Saharan Africa, this targeted investigation in sub-Saharan Africa has thus produced a centralized source of information on this subject for both African and global health policymakers. However, our results have also highlighted some key issues regarding the state of research on this subject within sub-Saharan Africa. First, studies were only identified across twelve total countries despite the fact that forty-eight countries were ultimately eligible for inclusion per our definition of sub-Saharan Africa; additionally, most of these included studies occurred in countries from Eastern and Southern Africa. This discrepancy thus emphasizes the need for more research from sub-Saharan African countries in order to more fully understand the impact of the COVID-19 pandemic on neonatal health outcomes in this region. Somewhat relatedly, among the sixteen final studies included in this systematic review and meta-analysis, only six of them were multi-national/national/regional investigations, thereby suggesting an overall lack of such studies in sub-Saharan Africa. Calvert et al.[7] also found a "paucity of population-based data in LMICs" and listed this dearth of associated information as a key challenge in determining the impact of COVID-19 mitigation measures in certain countries. We therefore recommend that African researchers take advantage of available national health information management systems (such as the District Health Information System 2, for example)[53,54] as well as other data sources (e.g., medical records from representative health facilities) in order to provide more national/regional investigations into this subject area. By addressing this overall lack of data as well as the specific lack of national/regional studies within sub-Saharan Africa, future investigations can help to further elucidate the impact of pandemic policies on neonatal health outcomes in sub-Saharan Africa and thus inform public health responses to future outbreaks of other infectious diseases that may require the introduction of similar mitigation measures.

Strengths and limitations

In support of our findings, the major strength of this study was the use of the systematic review and meta-analysis framework. More specifically, the use of such methodology provided a more objective approach than the traditional narrative review format due to the use of both a systematic approach and general transparency in the research methods. Moreover, the inference with regard to study selection was based on standardized criteria and thus not biased by any pre-conceived notions.[55] Additionally, the use of meta-analytical methods increased statistical power by combining individual studies, (potentially) improved generalizability via the inclusion of diverse populations, and allowed for the exploration of key subgroups of interest.[55,56] Furthermore, the inclusion of AJOL, AIM, and the WHO COVID-19 Database enabled the capture of additional studies specific to the sub-Saharan African context that would not have been identified if only more "traditional" databases (i.e., PubMed/MEDLINE, Embase, and Web of Sciences) were used. Additionally, the study setting (i.e., sub-Saharan Africa) represented another strength of this analysis due to the fact that the burden of adverse birth outcomes is much higher in sub-Saharan Africa than in other regions of the world;[23–25] thus, this high adverse birth outcome rate allowed for the detection of potentially minor changes during the imposition of COVID-19 mitigation measures.

Nevertheless, there were several limitations of this investigation that must also be considered. For example, methodological issues (e.g., selection bias and information bias) that plagued the included studies may have also impacted and therefore compromised the overall conclusions of this systematic review and meta-analysis (i.e., as a result of the "garbage in, garbage out" phenomenon).[57] Although we utilized the ROBINS-I tool to assess the quality of the included studies, we ultimately chose not to remove the four studies considered to be at serious/critical risk of bias since there were so few studies (i.e., only eleven for stillbirth, five for LBW, and six for PTB) included in our final list of records. In a similar vein, we categorized the study from Chapter 3 to be at moderate risk of bias; however, it should be acknowledged that such an assessment might not have been completely objective due to the fact that we authored Chapter 3. Moreover, we had no way of measuring the enforcement of/adherence to COVID-19 mitigation measures in the included countries; as a result, our conclusions must be caveated by the fact that these policies may have been imperfectly enforced by the government and/or received by the general population. Somewhat relatedly, although the use of the Oxford COVID-19 Government Response Tracker stringency score enabled us to apply a standardized metric of COVID-19 mitigation measures strength across the included studies, it should be noted that the Oxford COVID-19 Government Response Tracker stringency score is a national metric; therefore, this approach likely resulted in information bias for studies that did not occur at the national level (as it possible that local mitigation measures could have been stricter/looser than the national policies).

Additionally, we were not able to assess publication bias for LBW or PTB due to the low number of corresponding studies; thus, we cannot rule out its presence. Similarly, though we visually and statistically assessed for publication bias associated with stillbirth, we cannot completely rule out the possibility of publication bias for this outcome as strong assumptions inform the basis of a symmetrical plot/the associated statistical tests.[39] Related to publication bias, time lag bias – "the rapid or delayed publication of research findings, depending on the nature and direction of the results" – and outcome reporting bias – "the selective reporting of some outcomes but not others, depending on the nature and direction of the results" – may have also impacted the validity of our conclusions.[57] Another limitation related to decisions regarding the data extraction process. More specifically, certain studies employed ITS methodology (e.g., Burt et al.[58] and Chimhuya et al.[48]) or a difference-in-differences (DID) approach (i.e., Caniglia et al.[8] and Okeke et al.[59]) in their primary analysis; however, in order to be eligible for quantitative synthesis, we had to extract their initial data and then generate estimates that were cruder than their original ITS/DID estimates, thereby potentially introducing some confounding. Nonetheless, it should be highlighted that the crude estimates that we calculated were generally in line with the original measures of association, so the amount of added bias was likely minimal. Relatedly, though we categorized Okeke et al.[59] as a survey study, it was in fact a large-scale survey among a national sample of women so could have been categorized as multi-national/national/regional study as well, thereby leading to some potential misclassification bias; nonetheless, when the stillbirth meta-analysis was rerun with Okeke et al.[59] categorized as a multi-national/national/regional study, the corresponding stratified RR did not substantively change (i.e., from 1.03 [95% CI: 0.97, 1.09] to 1.06 [0.98; 1.15]).

Furthermore, sub-Saharan Africa is not a monolith but rather a large, diverse region of the world with a wide variety of different populations, cultures, practices, and healthcare systems; therefore, it should be acknowledged that the conclusions drawn here may not necessarily apply for the entire region. Moreover, meta-analyses ultimately represent analyses at the ecological level;[60,61] thus, we were only able to make observations about how COVID-19 mitigation measures impacted adverse birth outcome rates at the ecological level (as opposed to the individual level). Lastly, though we attempted to create a broad search strategy through the use of AJOL, AIM, and the WHO COVID-19 Database, our strategy was potentially limited by the fact that we did not translate our search terms into other languages (e.g., French and Portuguese) or include non-

English databases; as a result, we potentially missed articles that were only published in languages other than English (with no corresponding English abstract) and/or deposited in non-English databases. This limitation may help to explain why so few studies were ultimately identified from Western and Central Africa (i.e., regions with several Francophone countries). We therefore recommend that future meta-analyses that target the sub-Saharan Africa region consider expanding the scope of their search and database strategy to ensure key populations are not accidentally excluded; indeed, future researchers in this area should strive to form international collaborations to assure that searches are properly tailored according to the local/linguistic context.

Conclusion

Notwithstanding these limitations, this systematic review and meta-analysis succeeded in assessing the impact of COVID-19 mitigation measures on the risk of select adverse birth outcomes (i.e., stillbirth, LBW, and PTB) in sub-Saharan Africa. Despite issues related to high levels of heterogeneity at the overall level, our results suggested that the risk of all three outcomes did not change after the imposition of COVID-19 mitigation measures when focusing on multi-national/national/regional investigations. Nonetheless, we hope that our findings provide key insights for African health officials and policymakers regarding the real-world effects of COVID-19 mitigation measures and spur continued research in this subject area so that a more complete picture of the impact of COVID-19 mitigation measures in sub-Saharan Africa can be formed.

4.6. Tables and Figures

Table 4.1. Summary of the relevant literature on the association between selected adverse birth outcomes (i.e., stillbirth, LBW, and PTB) and COVID-19 mitigation measures in sub-Saharan Africa

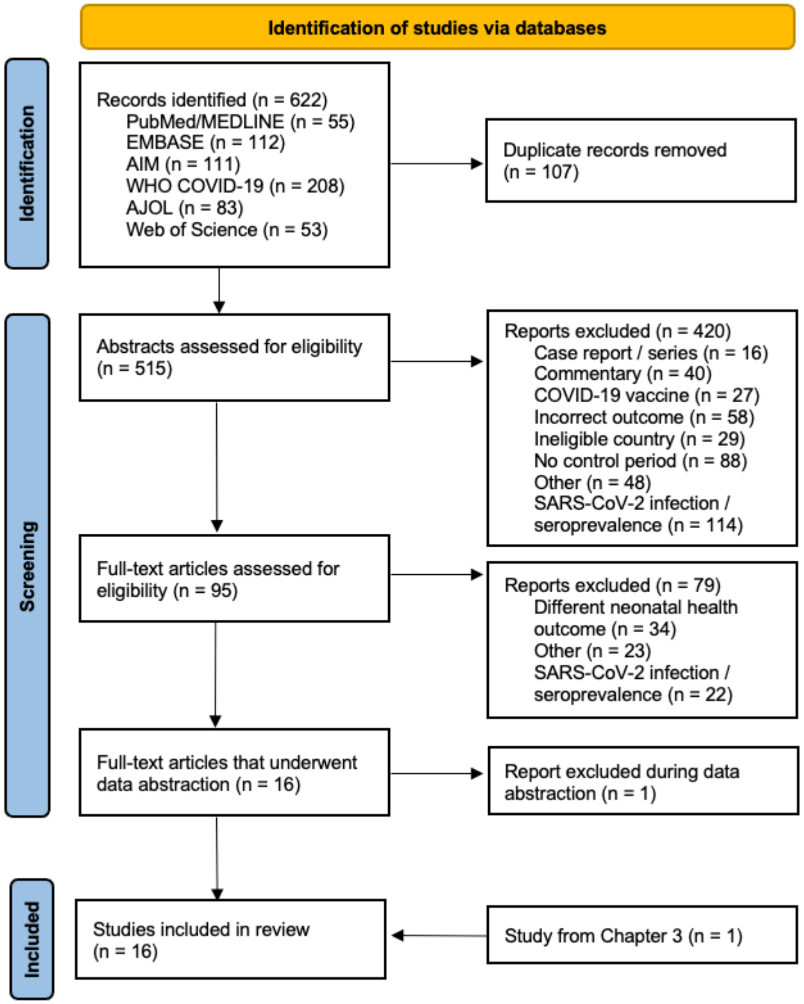
Author	Location	World Bank Economic Classification	AU Regional Group	Study Design	Type of Control Period	Mean (Range) National Stringency Score	Outcome(s)		
							Stillbirth	LBW	PTB
Abdul-Mumin[62]	Ghana	Lower middle-income	Western Africa	Single-center	Historical control	56.5 (2.8, 84.3)		✓	§
Arena[34]	DRC	Low-income	Central Africa	Regional	Immediately prior to exposure	69.3 (11.1, 80.6)	✓	✓	✓
Bikwa[63]	Zimbabwe	Lower middle-income	Southern Africa	Multi-center	Historical control	72.4 (8.3, 88.0)	✓		
Burt[58]	Uganda	Low-income	Eastern Africa	Single-center	Immediately prior to exposure	77.3 (52.8, 93.5)	✓	✓	¶
Caniglia[8]	Botswana	Upper middle-income	Southern Africa	National	Historical control	70.1 (57.4, 86.1)	✓		✓
Carter[64]	Ethiopia	Low-income	Eastern Africa	Survey	Immediately prior to exposure	80.6 (80.6, 80.6)	✓		
Chimhuya*[48]	Malawi	Low-income	Southern Africa	Single-center	Immediately prior to exposure	59.9 (52.8, 64.8)		✓	✓
	Zimbabwe	Lower middle-income	Southern Africa	Single-center	Immediately prior to exposure	79.4 (27.8, 88.0)		✓	✓

Author	Location	World Bank Economic Classification	AU Regional Group	Study Design	Type of Control Period	Mean (Range) National Stringency Score	Outcome(s)		
							Stillbirth	LBW	PTB
Desta[65]	Ethiopia	Low-income	Eastern Africa	Regional	Historical control	79.5 (66.7, 80.6)	✓		
Ezenwa[51]	Nigeria	Lower middle-income	Western Africa	Single-center	Historical control	84.1 (82.9, 85.7)			✓
Farley[66]	South Africa	Upper middle-income	Southern Africa	Survey	Immediately prior to exposure	77.3 (50.9, 88.0)			✓
Kassie[9]	Ethiopia	Low-income	Eastern Africa	Multi-center	Historical control	65.8 (2.8, 80.6)	✓		
Lydon[47]	Mozambique	Low-income	Southern Africa	Regional	Immediately prior to exposure	60.9 (50.0, 80.6)	✓		
Naqvi[†52]	DRC, Kenya, & Zambia	Low-income, Lower middle-income, & Low-income	Central, Eastern, & Southern Africa	Multi-national	Historical control	53.8 (2.8, 88.9)	✓	✓	✓
Okeke[59]	Nigeria	Lower middle-income	Western Africa	Survey	Immediately prior to exposure	70.6 (50.9, 85.7)	✓		‡
Shakespeare[10]	Zimbabwe	Lower middle-income	Southern Africa	Single-center	Immediately prior to exposure	83.7 (73.2, 88.0)	✓		
Shikuku[67]	Kenya	Lower middle-income	Eastern Africa	National	Historical control	77.5 (13.9, 88.9)	✓		

AU = African Union, DRC = Democratic Republic of the Congo, LBW = low birth weight, PTB = preterm birth.

*This study reported their analyses by country so have reported them separately here. †This study did not separate their results by country but instead presented them as an aggregated "Africa" category. As a result, World Bank Economic Classification and AU Regional Group information are provided for all three countries; however, for Mean (Range) National Stringency Score, the average and range across the three countries is presented. [§]PTB was evaluated in this study but was combined with other outcomes into the variable "prematurity and complications;" thus, the corresponding results for PTB have not been included due to concerns over potential misclassification. [¶]PTB was evaluated in this study, but due to the closure of the neonatal unit for refurbishment during the control period, it was not able to be properly recorded during several control period months; thus, the corresponding results for PTB have not been included. [‡]This study performed a sub-analysis of "earlier-than-expected births" to serve as a proxy for PTB; however, after reaching out to the study author for more information, they stated that this measure would not be suitable for this meta-analysis, so the corresponding results have not been included.

Figure 4.1. PRISMA flow diagram for systematic reviews



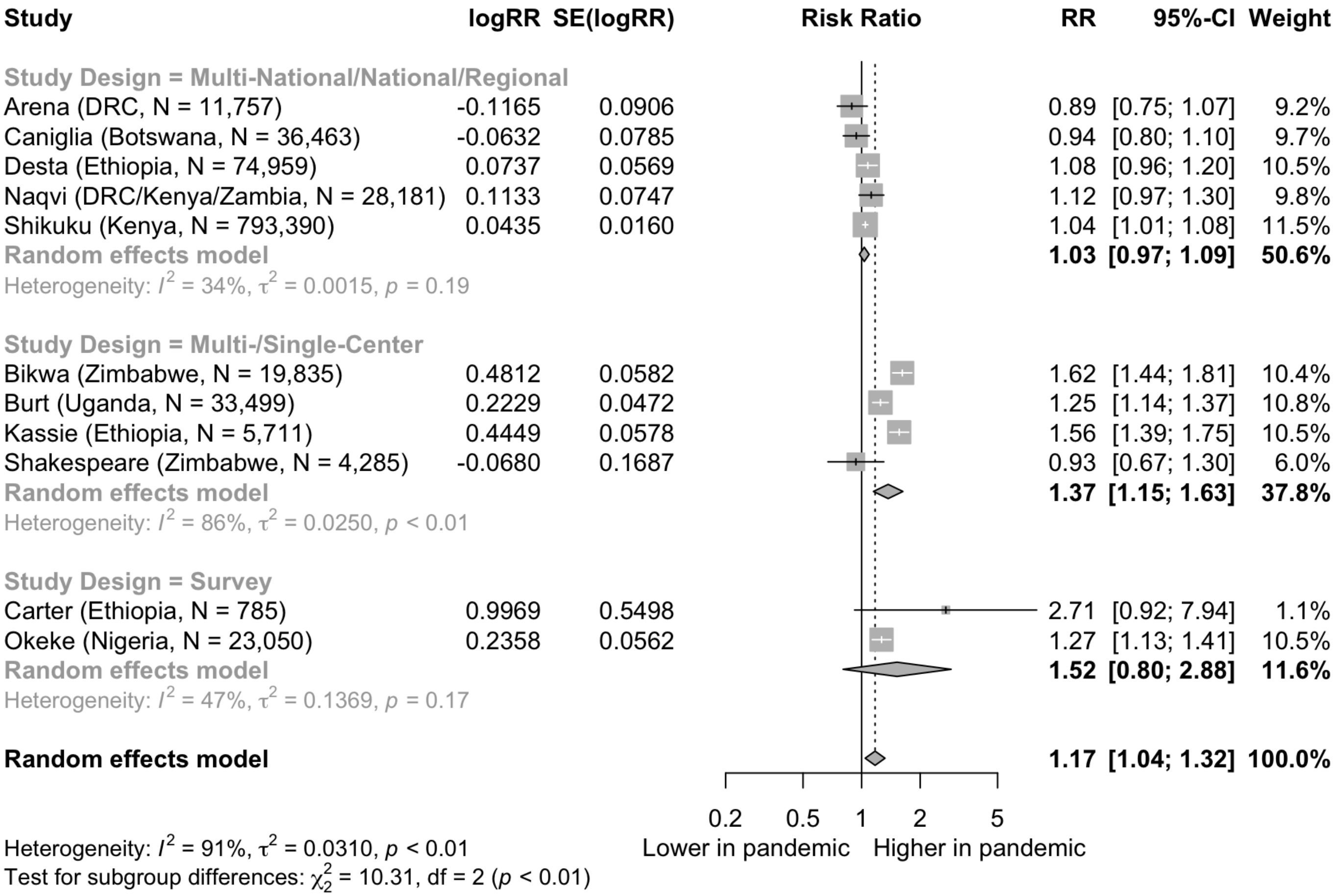
AIM = African Index Medicus, AJOL = African Journals Online, MEDLINE = Medical Literature Analysis and Retrieval System Online, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2, WHO = World Health Organization.

Based on template recommended by Page et al.[68]

Figure 4.2. Geographic summary of the included studies

Countries in blue refer to countries in which an identified study was performed, while n refers to the number of studies that occurred within a given country. Countries in gray were not eligible for inclusion (as they represent countries from the Northern Africa region).

Figure 4.3. Random-effects meta-analysis assessing the impact of COVID-19 mitigation measures on the risk of stillbirth in sub-Saharan Africa, overall and stratified by study design

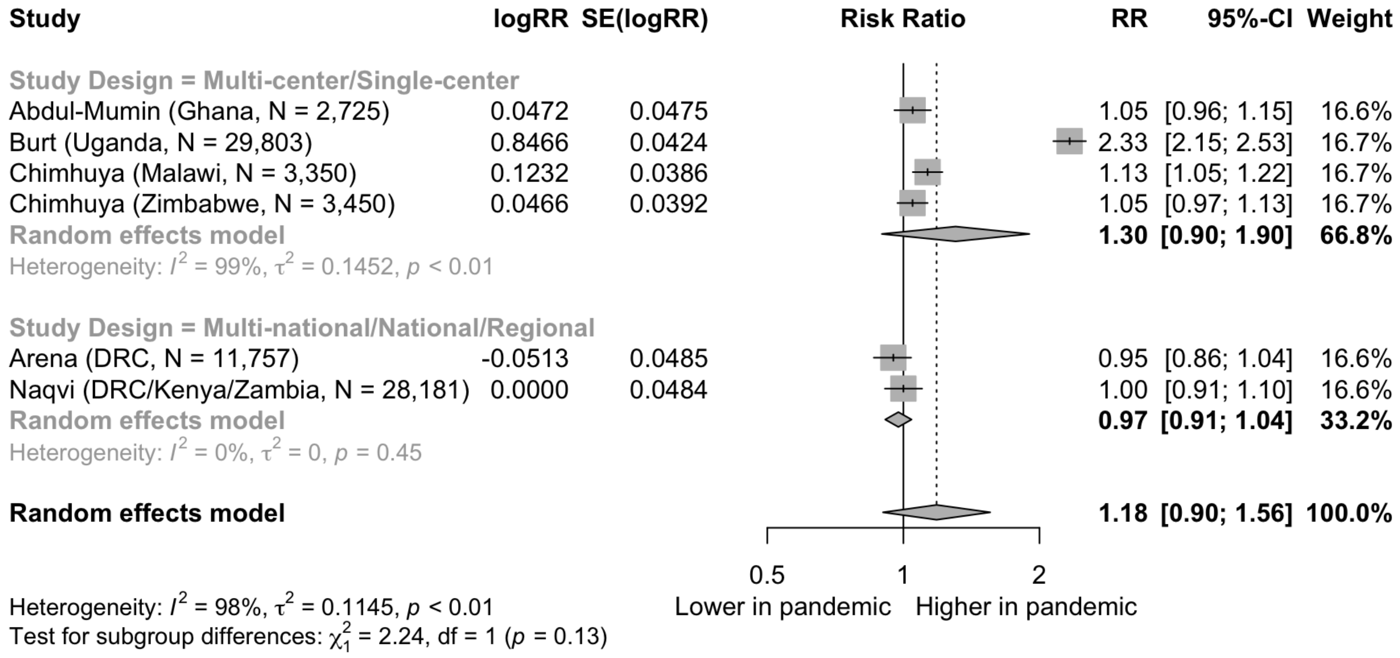


Study	logRR	SE(logRR)	RR	95%-CI	Weight
Study Design = Multi-National/National/Regional					
Arena (DRC, N = 11,757)	-0.1165	0.0906	0.89	[0.75; 1.07]	9.2%
Caniglia (Botswana, N = 36,463)	-0.0632	0.0785	0.94	[0.80; 1.10]	9.7%
Desta (Ethiopia, N = 74,959)	0.0737	0.0569	1.08	[0.96; 1.20]	10.5%
Naqvi (DRC/Kenya/Zambia, N = 28,181)	0.1133	0.0747	1.12	[0.97; 1.30]	9.8%
Shikuku (Kenya, N = 793,390)	0.0435	0.0160	1.04	[1.01; 1.08]	11.5%
Random effects model			**1.03**	**[0.97; 1.09]**	**50.6%**
Heterogeneity: $I^2 = 34\%$, $\tau^2 = 0.0015$, $p = 0.19$					
Study Design = Multi-/Single-Center					
Bikwa (Zimbabwe, N = 19,835)	0.4812	0.0582	1.62	[1.44; 1.81]	10.4%
Burt (Uganda, N = 33,499)	0.2229	0.0472	1.25	[1.14; 1.37]	10.8%
Kassie (Ethiopia, N = 5,711)	0.4449	0.0578	1.56	[1.39; 1.75]	10.5%
Shakespeare (Zimbabwe, N = 4,285)	-0.0680	0.1687	0.93	[0.67; 1.30]	6.0%
Random effects model			**1.37**	**[1.15; 1.63]**	**37.8%**
Heterogeneity: $I^2 = 86\%$, $\tau^2 = 0.0250$, $p < 0.01$					
Study Design = Survey					
Carter (Ethiopia, N = 785)	0.9969	0.5498	2.71	[0.92; 7.94]	1.1%
Okeke (Nigeria, N = 23,050)	0.2358	0.0562	1.27	[1.13; 1.41]	10.5%
Random effects model			**1.52**	**[0.80; 2.88]**	**11.6%**
Heterogeneity: $I^2 = 47\%$, $\tau^2 = 0.1369$, $p = 0.17$					
Random effects model			**1.17**	**[1.04; 1.32]**	**100.0%**

Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.0310$, $p < 0.01$
Test for subgroup differences: $\chi^2_2 = 10.31$, df = 2 ($p < 0.01$)

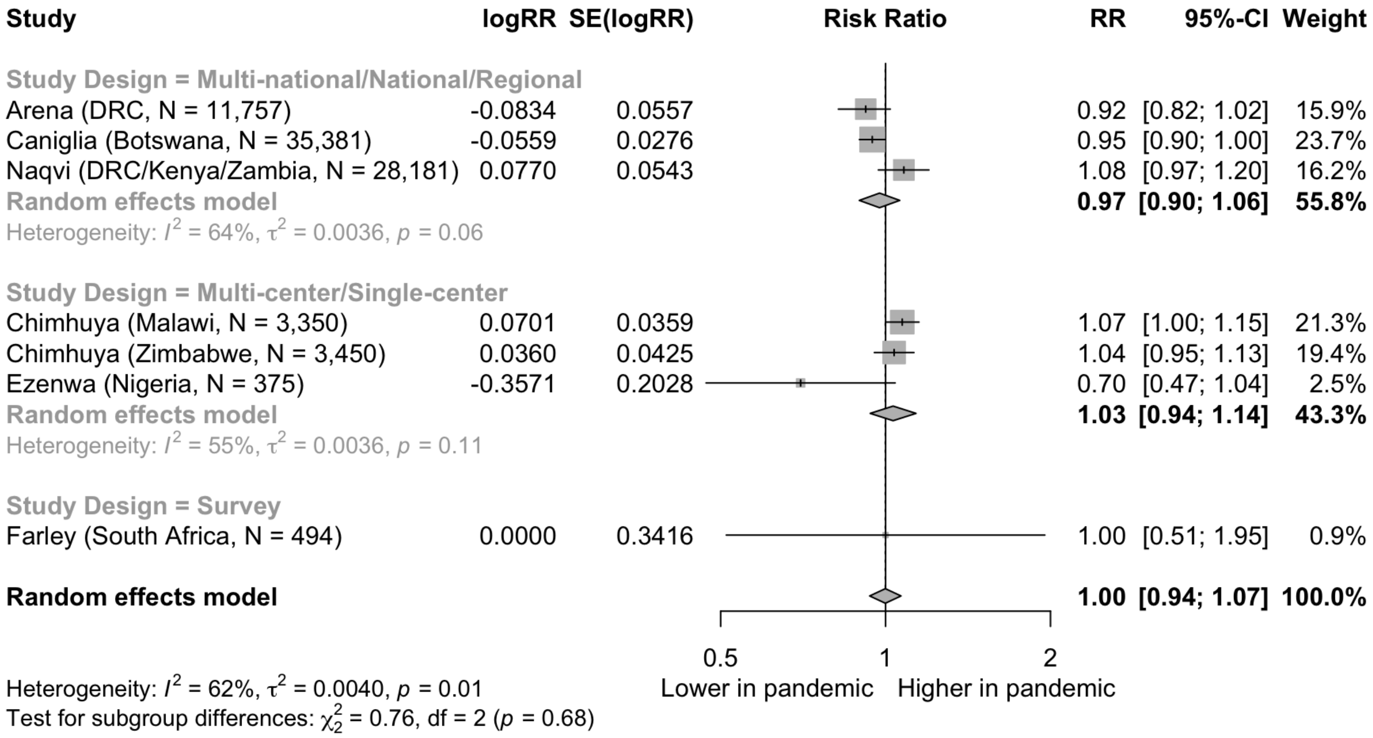
DRC = Democratic Republic of the Congo, RR = risk ratio.

Figure 4.4. Random-effects meta-analysis assessing the impact of COVID-19 mitigation measures on the risk of LBW in sub-Saharan Africa, overall and stratified by study design



DRC = Democratic Republic of the Congo, LBW = low birth weight, RR = risk ratio.

Figure 4.5. Random-effects meta-analysis assessing the impact of COVID-19 mitigation measures on the risk of PTB in sub-Saharan Africa, overall and stratified by study design



Study	logRR	SE(logRR)	RR	95%-CI	Weight
Study Design = Multi-national/National/Regional					
Arena (DRC, N = 11,757)	-0.0834	0.0557	0.92	[0.82; 1.02]	15.9%
Caniglia (Botswana, N = 35,381)	-0.0559	0.0276	0.95	[0.90; 1.00]	23.7%
Naqvi (DRC/Kenya/Zambia, N = 28,181)	0.0770	0.0543	1.08	[0.97; 1.20]	16.2%
Random effects model			**0.97**	**[0.90; 1.06]**	**55.8%**
Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.0036$, $p = 0.06$					
Study Design = Multi-center/Single-center					
Chimhuya (Malawi, N = 3,350)	0.0701	0.0359	1.07	[1.00; 1.15]	21.3%
Chimhuya (Zimbabwe, N = 3,450)	0.0360	0.0425	1.04	[0.95; 1.13]	19.4%
Ezenwa (Nigeria, N = 375)	-0.3571	0.2028	0.70	[0.47; 1.04]	2.5%
Random effects model			**1.03**	**[0.94; 1.14]**	**43.3%**
Heterogeneity: $I^2 = 55\%$, $\tau^2 = 0.0036$, $p = 0.11$					
Study Design = Survey					
Farley (South Africa, N = 494)	0.0000	0.3416	1.00	[0.51; 1.95]	0.9%
Random effects model			**1.00**	**[0.94; 1.07]**	**100.0%**

Heterogeneity: $I^2 = 62\%$, $\tau^2 = 0.0040$, $p = 0.01$

Test for subgroup differences: $\chi^2_2 = 0.76$, df = 2 ($p = 0.68$)

DRC = Democratic Republic of the Congo, PTB = preterm birth, RR = risk ratio.

4.7. Appendix

Supplemental Table 4.1. Search strategy for PubMed/MEDLINE

PICO category	Associated concept	PubMed/MEDLINE Search Terms
Population	Pregnant women and their newborns in sub-Saharan Africa during the intervention period†	(("Angola"[Mesh] OR "Angola"[Title/Abstract]) OR ("Benin"[Mesh] OR "Benin"[Title/Abstract]) OR ("Botswana"[Mesh] OR "Botswana"[Title/Abstract]) OR ("Burkina Faso"[Mesh] OR "Burkina Faso"[Title/Abstract]) OR ("Burundi"[Mesh] OR "Burundi"[Title/Abstract]) OR ("Cameroon"[Mesh] OR "Cameroon"[Title/Abstract]) OR ("Cabo Verde"[Mesh] OR "Cabo Verde"[Title/Abstract] OR "Cape Verde"[Title/Abstract]) OR ("Central African Republic"[Mesh] OR "Central African Republic"[Title/Abstract]) OR ("Chad"[Mesh] OR "Chad"[Title/Abstract]) OR ("Comoros"[Mesh] OR "Comoros"[Title/Abstract]) OR ("Cote d'Ivoire"[Mesh] OR "Cote d'Ivoire"[Title/Abstract] OR "Ivory Coast"[Title/Abstract]) OR ("Democratic Republic of the Congo"[Mesh] OR "Democratic Republic of the Congo"[Title/Abstract] OR "Congo"[Title/Abstract] OR "Kinshasa"[Title/Abstract]) OR ("Djibouti"[Mesh] OR "Djibouti"[Title/Abstract]) OR ("Equatorial Guinea"[Mesh] OR "Equatorial Guinea"[Title/Abstract]) OR ("Eritrea"[Mesh] OR "Eritrea"[Title/Abstract]) OR ("Ethiopia"[Mesh] OR "Ethiopia"[Title/Abstract]) OR ("Gabon"[Mesh] OR "Gabon"[Title/Abstract]) OR ("Gambia"[Mesh] OR "Gambia"[Title/Abstract]) OR ("Ghana"[Mesh] OR "Ghana"[Title/Abstract]) OR ("Guinea"[Mesh] OR "Conakry"[Title/Abstract] OR "French Guinea"[Title/Abstract]) OR ("Guinea-Bissau"[Mesh] OR "Bissau"[Title/Abstract] OR "Portuguese Guinea"[Title/Abstract]) OR ("Kenya"[Mesh] OR "Kenya"[Title/Abstract]) OR ("Lesotho"[Mesh] OR "Lesotho"[Title/Abstract]) OR

PICO category	Associated concept	PubMed/MEDLINE Search Terms
		("Liberia"[Mesh] OR "Liberia"[Title/Abstract]) OR ("Madagascar"[Mesh] OR "Madagascar"[Title/Abstract]) OR ("Malawi"[Mesh] OR "Malawi"[Title/Abstract]) OR ("Mali"[Mesh] OR "Mali"[Title/Abstract]) OR ("Mauritius"[Mesh] OR "Mauritius"[Title/Abstract]) OR ("Mozambique"[Mesh] OR "Mozambique"[Title/Abstract]) OR ("Namibia"[Mesh] OR "Namibia"[Title/Abstract]) OR ("Niger"[Mesh] OR "Niger"[Title/Abstract]) OR ("Nigeria"[Mesh] OR "Nigeria"[Title/Abstract]) OR ("Congo"[Mesh] OR "Congo"[Title/Abstract] OR "Republic of Congo"[Title/Abstract] OR "Brazzaville"[Title/Abstract]) OR ("Rwanda"[Mesh] OR "Rwanda"[Title/Abstract]) OR ("Sao Tome and Principe"[Mesh] OR "Sao Tome and Principe"[Title/Abstract] OR "São Tomé and Principe"[Title/Abstract]) OR ("Senegal"[Mesh] OR "Senegal"[Title/Abstract]) OR ("Seychelles"[Mesh] OR "Seychelles"[Title/Abstract]) OR ("Sierra Leone"[Mesh] OR "Sierra Leone"[Title/Abstract]) OR ("Somalia"[Mesh] OR "Somalia"[Title/Abstract]) OR ("South Africa"[Mesh] OR "South Africa"[Title/Abstract]) OR ("South Sudan"[Mesh] OR "South Sudan"[Title/Abstract]) OR ("Sudan"[Mesh] OR "Sudan"[Title/Abstract]) OR ("Eswatini"[Mesh] OR "Eswatini"[Title/Abstract] OR "Swaziland"[Title/Abstract]) OR ("Tanzania"[Mesh] OR "Tanzania"[Title/Abstract]) OR ("Togo"[Mesh] OR "Togo"[Title/Abstract]) OR ("Uganda"[Mesh] OR "Uganda"[Title/Abstract]) OR ("Zambia"[Mesh] OR "Zambia"[Title/Abstract]) OR ("Zimbabwe"[Mesh] OR "Zimbabwe"[Title/Abstract]))
Intervention	COVID-19 mitigation measures*	("COVID-19"[Mesh] OR "COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "COVID 19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "2019 Novel Coronavirus"[Title/Abstract] OR "2019 nCoV"[Title/Abstract] OR "Coronavirus Disease"[Title/Abstract] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[Title/Abstract] OR "SARS Coronavirus 2"[Title/Abstract] OR "pandemic"[Title/Abstract] OR "Wuhan virus"[Title/Abstract])

PICO category	Associated concept	PubMed/MEDLINE Search Terms
Comparator	Pregnant women and their newborns in sub-Saharan Africa during a period prior to the intervention	*Not applicable – however, all identified studies were screened to ensure that they used some form of a pre-COVID-19 comparison period.*
Outcome(s)	Stillbirth, LBW, and/or PTB	(((("premature birth"[MeSH Terms] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR "preterm"[All Fields] OR "preterms"[All Fields] OR "obstetric labor, premature"[MeSH Terms] OR ("obstetric"[All Fields] AND "labor"[All Fields] AND "premature"[All Fields]) OR "premature obstetric labor"[All Fields] OR ("preterm"[All Fields] AND "labor"[All Fields]) OR "preterm labor"[All Fields] OR "premature"[All Fields] OR "prematurely"[All Fields] OR "prematures"[All Fields] OR "prematurities"[All Fields] OR "prematurity"[All Fields] OR "premature labour"[All Fields]) OR ("infant, low birth weight"[MeSH Terms] OR ("infant"[All Fields] AND "low"[All Fields] AND "birth"[All Fields] AND "weight"[All Fields]) OR "low birth weight infant"[All Fields] OR ("low"[All Fields] AND "birthweight"[All Fields]) OR "low birthweight"[All Fields] OR ("low"[All Fields] AND "birth"[All Fields] AND "weight"[All Fields]) OR "low birth weight"[All Fields])) OR ("stillbirth"[MeSH Terms] OR "stillbirth"[All Fields] OR ("still"[All Fields] AND "birth"[All Fields]) OR "still birth"[All Fields] OR "stillbirths"[All Fields] OR "stillborn"[All Fields] OR "stillborns"[All Fields])) OR ("Premature Birth"[Mesh] OR "Premature Birth"[all] OR "Preterm Birth"[all] OR "Premature Infant"[all] OR "Preterm Infant"[all] OR "Prematurity"[all] OR "Preterm labour"[all] OR "Preterm labor"[all] OR "Premature labor"[all] OR "Premature labour"[all] OR "Preterm Delivery"[all] OR "Premature Delivery"[all]) OR ("Stillbirth"[Mesh] OR "Stillbirth"[all] OR "Still birth"[all] OR "Stillborn"[all] OR "Still born"[all]) OR ("Infant, Low Birth Weight"[Mesh] OR "Low Birth Weight"[all] OR "Low Birthweight"[all] OR "Low-Birth-Weight"[all]))

LBW = low birth weight, MEDLINE = Medical Literature Analysis and Retrieval System Online, PICO = Population, intervention, comparator, and outcome, PTB = preterm birth.

[†]Because the outcomes (i.e., LBW, stillbirth, and PTB) only occur among newborns, no additional terms for "pregnant women and their newborns" were added to the searches. [*]Since there is a wide variety in the terms used to describe COVID-19 mitigation measures (i.e., lockdown, quarantine, isolation, stay-at-home orders, mask mandates, etc.), terms for "COVID-19" were used and then selected articles were screened to only include instances where pregnant women and their newborns were compared during and prior to the imposition of COVID-19 mitigation measures.

Supplemental Table 4.2. Search strategy for Embase

PICO category	Associated concept	Embase Search Terms
Population	Pregnant women and their newborns in sub-Saharan Africa during the intervention period[†]	'africa south of the sahara'/exp OR 'africa south of the sahara' OR 'angola'/exp OR 'angola' OR 'angola':ab,ti OR 'benin'/exp OR 'benin' OR 'benin':ab,ti OR 'botswana'/exp OR 'botswana' OR 'botswana':ab,ti OR 'burkina faso'/exp OR 'burkina faso' OR 'burkina faso':ab,ti OR 'burundi'/exp OR 'burundi' OR 'burundi':ab,ti OR 'cameroon'/exp OR 'cameroon' OR 'cameroon':ab,ti OR 'cape verde'/exp OR 'cape verde' OR 'cape verde':ab,ti OR 'cabo verde':ab,ti OR 'central african republic'/exp OR 'central african republic' OR 'central african republic':ab,ti OR 'chad'/exp OR 'chad' OR 'chad':ab,ti OR 'comoros'/exp OR 'comoros' OR 'comoros':ab,ti OR 'congo'/exp OR 'congo' OR 'congo':ab,ti OR 'brazzaville':ab,ti OR 'cote d`ivoire'/exp OR 'cote d`ivoire' OR 'cote d`ivoire':ab,ti OR 'ivory coast':ab,ti OR 'democratic republic congo'/exp OR 'democratic republic congo' OR 'democratic republic congo':ab,ti OR 'kinshasa':ab,ti OR 'djibouti'/exp OR 'djibouti' OR 'djibouti':ab,ti OR 'equatorial guinea'/exp OR 'equatorial guinea' OR 'equatorial guinea':ab,ti OR 'eritrea'/exp OR 'eritrea' OR 'eritrea':ab,ti OR 'eswatini'/exp OR 'eswatini' OR 'eswatini':ab,ti OR 'swaziland':ab,ti OR 'ethiopia'/exp OR 'ethiopia' OR 'ethiopia':ab,ti OR 'gabon'/exp OR 'gabon' OR 'gabon':ab,ti OR 'gambia'/exp OR 'gambia' OR 'gambia':ab,ti OR 'ghana'/exp OR 'ghana' OR 'ghana':ab,ti OR 'guinea'/exp OR 'guinea' OR 'guinea':ab,ti OR 'conakry':ab,ti OR 'french guinea':ab,ti OR 'guinea-bissau'/exp OR 'guinea-bissau' OR 'guinea-bissau':ab,ti OR 'bissau':ab,ti OR 'portuguese guinea':ab,ti OR 'kenya'/exp OR 'kenya' OR 'kenya':ab,ti OR 'lesotho'/exp OR 'lesotho' OR 'lesotho':ab,ti OR 'liberia'/exp OR 'liberia' OR 'liberia':ab,ti OR 'madagascar'/exp OR 'madagascar' OR 'madagascar':ab,ti OR 'malawi'/exp OR 'malawi' OR 'malawi':ab,ti OR 'mali'/exp OR 'mali' OR 'mali':ab,ti OR 'mauritius':ab,ti OR 'mozambique'/exp OR 'mozambique' OR 'mozambique':ab,ti OR 'namibia'/exp OR 'namibia' OR 'namibia':ab,ti OR 'niger'/exp OR 'niger' OR 'niger':ab,ti OR 'nigeria'/exp OR 'nigeria' OR 'nigeria':ab,ti OR 'rwanda'/exp OR 'rwanda' OR 'rwanda':ab,ti OR 'senegal'/exp OR 'senegal' OR 'senegal':ab,ti OR 'seychelles':ab,ti OR 'sierra leone'/exp OR 'sierra leone' OR 'sierra leone':ab,ti OR 'sao tome and principe':ab,ti OR 'são tomé and principe':ab,ti OR 'somalia'/exp OR 'somalia' OR 'somalia':ab,ti OR 'south africa'/exp OR 'south africa' OR 'south africa':ab,ti OR 'south sudan'/exp OR 'south sudan' OR 'south sudan':ab,ti OR 'sudan'/exp OR 'sudan' OR 'sudan':ab,ti OR 'tanzania'/exp OR 'tanzania' OR 'tanzania':ab,ti OR 'togo'/exp OR

PICO category	Associated concept	Embase Search Terms
		'togo' OR 'togo':ab,ti OR 'uganda'/exp OR 'uganda' OR 'uganda':ab,ti OR 'zambia'/exp OR 'zambia' OR 'zambia':ab,ti OR 'zimbabwe'/exp OR 'zimbabwe' OR 'zimbabwe':ab,ti
Intervention	COVID-19 mitigation measures*	'coronavirus disease 2019'/exp OR 'coronavirus disease 2019':ab,ti,kw OR 'covid-19':ab,ti,kw OR 'covid 19':ab,ti,kw OR 'covid19':ab,ti,kw OR 'sars-cov-2':ab,ti,kw OR '2019 novel coronavirus':ab,ti,kw OR '2019 ncov':ab,ti,kw OR 'coronavirus disease':ab,ti,kw OR 'severe acute respiratory syndrome coronavirus 2':ab,ti,kw OR 'sars coronavirus 2':ab,ti,kw OR 'pandemic':ab,ti,kw OR 'wuhan virus':ab,ti,kw
Comparator	Pregnant women and their newborns in sub-Saharan Africa during a period prior to the intervention	*Not applicable – however, all identified studies were screened to ensure that they used some form of a pre-COVID-19 comparison period.*
Outcome(s)	Stillbirth, LBW, and/or PTB	'low birth weight'/exp OR 'low birth weight' OR 'low birth weight':ab,ti,kw OR 'low birthweight':ab,ti,kw OR 'low-birth-weight':ab,ti,kw OR 'stillbirth'/exp OR 'stillbirth' OR 'stillbirth':ab,ti,kw OR 'still birth':ab,ti,kw OR 'stillborn':ab,ti,kw OR 'still born':ab,ti,kw OR 'prematurity'/exp OR 'prematurity' OR 'prematurity':ab,ti,kw OR 'premature birth':ab,ti,kw OR 'premature infant':ab,ti,kw OR 'preterm birth':ab,ti,kw OR 'preterm infant':ab,ti,kw OR 'preterm delivery':ab,ti,kw OR 'premature delivery':ab,ti,kw OR 'preterm labor':ab,ti,kw OR 'preterm labour':ab,ti,kw OR 'premature labor':ab,ti,kw OR 'premature labour':ab,ti,kw

LBW = low birth weight, PICO = Population, intervention, comparator, and outcome, PTB = preterm birth.

†Because the outcomes (i.e., LBW, stillbirth, and PTB) only occur among newborns, no additional terms for "pregnant women and their newborns" were added to the searches. *Since there is a wide variety in the terms used to describe COVID-19 mitigation measures (i.e., lockdown, quarantine, isolation, stay-at-home orders, mask mandates, etc.), terms for "COVID-19" were used and then selected articles were screened to only include instances where pregnant women and their newborns were compared during and prior to the imposition of COVID-19 mitigation measures.

Supplemental Table 4.3. Search strategy for Web of Science

PICO category	Associated concept	Web of Science Search Terms
Population	Pregnant women and their newborns in sub-Saharan Africa during the intervention period†	((ALL=("ANGOLA")) OR ALL=("Benin")) OR ALL=("Botswana")) OR ALL=("Burkina Faso")) OR ALL=("Burundi")) OR ALL=("Cameroon")) OR ALL=("Cape Verde")) OR ALL=("Cabo Verde")) OR ALL=("Central African Republic")) OR ALL=("Chad")) OR ALL=("Comoros")) OR ALL=("Congo")) OR ALL=("Brazzaville")) OR ALL=("Cote d`Ivoire")) OR ALL=("Ivory Coast")) OR ALL=("Democratic Republic Congo")) OR ALL=("Democratic Republic of Congo")) OR ALL=("Kinshasa")) OR ALL=("Djibouti")) OR ALL=("Equatorial Guinea")) OR ALL=("Eritrea")) OR ALL=("Eswatini")) OR ALL=("Swaziland")) OR ALL=("Ethiopia")) OR ALL=("Gabon")) OR ALL=("Gambia")) OR ALL=("Ghana")) OR ALL=("Guinea")) OR ALL=("Conakry")) OR ALL=("Guinea-Bissau")) OR ALL=("Bissau")) OR ALL=("Kenya")) OR ALL=("Lesotho")) OR ALL=("Liberia")) OR ALL=("Madagascar")) OR ALL=("Mali")) OR ALL=("Mauritius")) OR ALL=("Mozambique")) OR ALL=("Namibia")) OR ALL=("Niger")) OR ALL=("Nigeria")) OR ALL=("Rwanda")) OR ALL=("Senegal")) OR ALL=("Seychelles")) OR ALL=("Sierra Leone")) OR ALL=("Principe")) OR ALL=("Somalia")) OR ALL=("South Africa")) OR ALL=("South Sudan")) OR ALL=("Sudan")) OR ALL=("Tanzania")) OR ALL=("Togo")) OR ALL=("Uganda")) OR ALL=("Zambia")) OR ALL=("Zimbabwe")
Intervention	COVID-19 mitigation measures*	(((((((((ALL=("COVID-19")) OR ALL=("COVID19")) OR ALL=("COVID 19")) OR ALL=("SARS-COV-2")) OR ALL=("2019 NOVEL CORONAVIRUS")) OR ALL=("2019 NCOV")) OR ALL=("CORONAVIRUS DISEASE")) OR ALL=("SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2")) OR ALL=("SARS CORONAVIRUS 2")) OR ALL=("PANDEMIC") OR ALL=("WUHAN VIRUS")
Comparator	Pregnant women and their newborns in sub-Saharan Africa during a period prior to the intervention	*Not applicable – however, all identified studies were screened to ensure that they used some form of a pre-COVID-19 comparison period.*

PICO category	Associated concept	Web of Science Search Terms
Outcome(s)	Stillbirth, LBW, and/or PTB	((((((((((((ALL=("low birth weight")) OR ALL=("low birthweight")) OR ALL=("low-birth-weight")) OR ALL=("stillbirth")) OR ALL=("still birth")) OR ALL=("stillborn")) OR ALL=("still born")) OR ALL=("premature birth")) OR ALL=("preterm birth")) OR ALL=("premature infant")) OR ALL=("preterm infant")) OR ALL=("prematurity") OR ALL=("preterm delivery") OR ALL=("premature delivery") OR ALL=("premature labor") OR ALL=("preterm labor") OR ALL=("premature labour") OR ALL=("preterm labour")

LBW = low birth weight, PICO = Population, intervention, comparator, and outcome, PTB = preterm birth.

†Because the outcomes (i.e., LBW, stillbirth, and PTB) only occur among newborns, no additional terms for “pregnant women and their newborns” were added to the searches. *Since there is a wide variety in the terms used to describe COVID-19 mitigation measures (i.e., lockdown, quarantine, isolation, stay-at-home orders, mask mandates, etc.), terms for “COVID-19” were used and then selected articles were screened to only include instances where pregnant women and their newborns were compared during and prior to the imposition of COVID-19 mitigation measures.

Supplemental Table 4.4. Search strategy for AJOL

PICO category	Associated concept	AJOL Search Terms
Population	Pregnant women and their newborns in sub-Saharan Africa during the intervention period†	*Not applicable – database is Africa-specific.*
Intervention	COVID-19 mitigation measures*	("COVID-19" OR "COVID19" OR "COVID 19" OR "SARS-COV-2" OR "2019 NOVEL CORONAVIRUS" OR "2019 NCOV" OR "CORONAVIRUS DISEASE" OR "SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2" OR "SARS CORONAVIRUS 2" OR "PANDEMIC")
Comparator	Pregnant women and their newborns in sub-Saharan Africa during a period prior to the intervention	*Not applicable – however, all identified studies were screened to ensure that they used some form of a pre-COVID-19 comparison period.*
Outcome(s)	Stillbirth, LBW, and/or PTB	("STILLBIRTH" OR “STILL BIRTH” OR “STILLBORN” OR “STILL BORN” OR "PRETERM BIRTH" OR “PREMATURE BIRTH” OR “PRETERM INFANT” OR “PREMATURE INFANT” OR “PREMATURITY” OR “PRETERM DELIVERY” OR “PREMATURE DELIVERY” OR “PRETERM LABOR” OR “PREMATURE LABOR” OR “PRETERM LABOUR” OR “PREMATURE LABOUR” OR "LOW BIRTH WEIGHT" OR “LOW BIRTHWEIGHT” OR “LOW-BIRTH-WEIGHT”)

AJOL = African Journals Online, LBW = low birth weight, PICO = Population, intervention, comparator, and outcome, PTB = preterm birth.
†Because the outcomes (i.e., LBW, stillbirth, and PTB) only occur among newborns, no additional terms for “pregnant women and their newborns” were added to the searches. *Since there is a wide variety in the terms used to describe COVID-19 mitigation measures (i.e., lockdown, quarantine, isolation, stay-at-home orders, mask mandates, etc.), terms for “COVID-19” were used and then selected articles were screened to only include instances where pregnant women and their newborns were compared during and prior to the imposition of COVID-19 mitigation measures.

Supplemental Table 4.5. Search strategy for AIM

PICO category	Associated concept	AIM Search Terms
Population	Pregnant women and their newborns in sub-Saharan Africa during the intervention period†	*Not applicable – database is Africa-specific.*
Intervention	COVID-19 mitigation measures*	("COVID-19" OR "COVID19" OR "COVID 19" OR "SARS-COV-2" OR "2019 NOVEL CORONAVIRUS" OR "2019 NCOV" OR "CORONAVIRUS DISEASE" OR "SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2" OR "SARS CORONAVIRUS 2" OR "PANDEMIC")
Comparator	Pregnant women and their newborns in sub-Saharan Africa during a period prior to the intervention	*Not applicable – however, all identified studies were screened to ensure that they used some form of a pre-COVID-19 comparison period.*
Outcome(s)	Stillbirth, LBW, and/or PTB	("STILLBIRTH" OR “STILL BIRTH” OR “STILLBORN” OR “STILL BORN” OR "PRETERM BIRTH" OR “PREMATURE BIRTH” OR “PRETERM INFANT” OR “PREMATURE INFANT” OR “PREMATURITY” OR “PRETERM DELIVERY” OR “PREMATURE DELIVERY” OR “PRETERM LABOR” OR “PREMATURE LABOR” OR “PRETERM LABOUR” OR “PREMATURE LABOUR” OR "LOW BIRTH WEIGHT" OR “LOW BIRTHWEIGHT” OR “LOW-BIRTH-WEIGHT”)

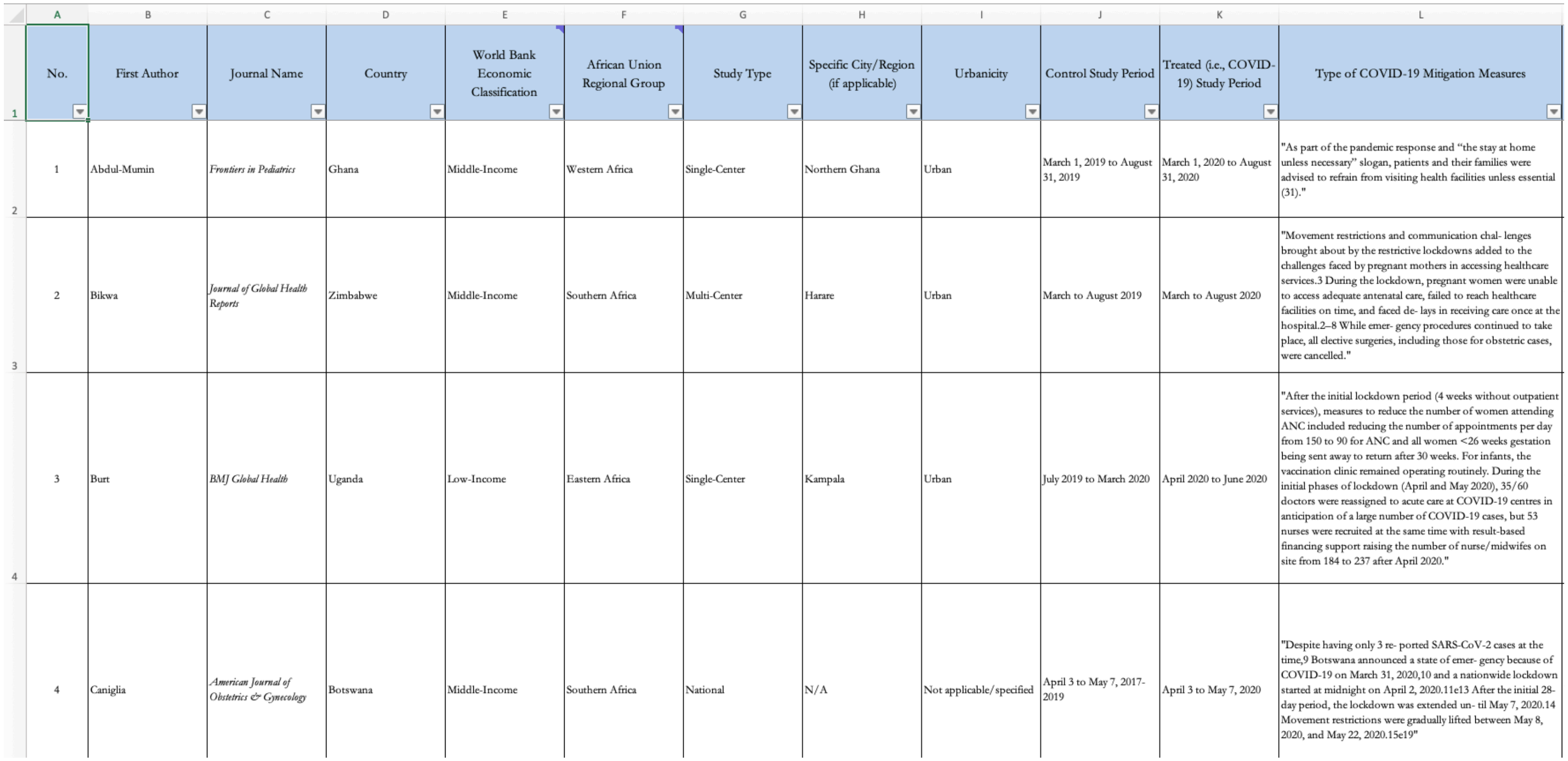
AIM = African Index Medicus, LBW = low birth weight, PICO = Population, intervention, comparator, and outcome, PTB = preterm birth.
†Because the outcomes (i.e., LBW, stillbirth, and PTB) only occur among newborns, no additional terms for “pregnant women and their newborns” were added to the searches. *Since there is a wide variety in the terms used to describe COVID-19 mitigation measures (i.e., lockdown, quarantine, isolation, stay-at-home orders, mask mandates, etc.), terms for “COVID-19” were used and then selected articles were screened to only include instances where pregnant women and their newborns were compared during and prior to the imposition of COVID-19 mitigation measures.

Supplemental Table 4.6. Search strategy for WHO COVID-19 Database

PICO category	Associated concept	WHO COVID-19 Database Search Terms
Population	Pregnant women and their newborns in sub-Saharan Africa during the intervention period†	(“Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cameroon” OR “Cape Verde” OR “Cabo Verde” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Congo” OR “Brazzaville” OR “Cote d`Ivoire” OR “Ivory Coast” OR “Democratic Republic Congo” OR “Democratic Republic of Congo” OR “Kinshasa” OR “Djibouti” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Swaziland” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Conakry” OR “French Guinea” OR “Guinea-Bissau” OR “Bissau” OR “Portuguese Guinea” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Principe” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” OR “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”)
Intervention	COVID-19 mitigation measures*	*Not applicable – database already filtered to only COVID-19 studies.*
Comparator	Pregnant women and their newborns in sub-Saharan Africa during a period prior to the intervention	*Not applicable – however, all identified studies were screened to ensure that they used some form of a pre-COVID-19 comparison period.*
Outcome(s)	Stillbirth, LBW, and/or PTB	("STILLBIRTH" OR “STILL BIRTH” OR “STILLBORN” OR “STILL BORN” OR "PRETERM BIRTH" OR “PREMATURE BIRTH” OR “PRETERM INFANT” OR “PREMATURE INFANT” OR “PREMATURITY” OR “PRETERM DELIVERY” OR “PREMATURE DELIVERY” OR “PRETERM LABOR” OR “PREMATURE LABOR” OR “PRETERM LABOUR” OR “PREMATURE LABOUR” OR "LOW BIRTH WEIGHT" OR “LOW BIRTHWEIGHT” OR “LOW-BIRTH-WEIGHT”)

LBW = low birth weight, PICO = Population, intervention, comparator, and outcome, PTB = preterm birth, WHO = World Health Organization.
†Because the outcomes (i.e., LBW, stillbirth, and PTB) only occur among newborns, no additional terms for “pregnant women and their newborns” were added to the searches. *Since there is a wide variety in the terms used to describe COVID-19 mitigation measures (i.e., lockdown, quarantine, isolation, stay-at-home orders, mask mandates, etc.), selected articles were screened to only include instances where pregnant women and their newborns were compared during and prior to the imposition of COVID-19 mitigation measures.

Supplemental Figure 4.1. Screenshot of (completed) standardized data extraction form



No.	First Author	Journal Name	Country	World Bank Economic Classification	African Union Regional Group	Study Type	Specific City/Region (if applicable)	Urbanicity	Control Study Period	Treated (i.e., COVID-19) Study Period	Type of COVID-19 Mitigation Measures
1	Abdul-Mumin	*Frontiers in Pediatrics*	Ghana	Middle-Income	Western Africa	Single-Center	Northern Ghana	Urban	March 1, 2019 to August 31, 2019	March 1, 2020 to August 31, 2020	"As part of the pandemic response and "the stay at home unless necessary" slogan, patients and their families were advised to refrain from visiting health facilities unless essential (31)."
2	Bikwa	*Journal of Global Health Reports*	Zimbabwe	Middle-Income	Southern Africa	Multi-Center	Harare	Urban	March to August 2019	March to August 2020	"Movement restrictions and communication chal- lenges brought about by the restrictive lockdowns added to the challenges faced by pregnant mothers in accessing healthcare services.3 During the lockdown, pregnant women were unable to access adequate antenatal care, failed to reach healthcare facilities on time, and faced de- lays in receiving care once at the hospital.2–8 While emer- gency procedures continued to take place, all elective surgeries, including those for obstetric cases, were cancelled."
3	Burt	*BMJ Global Health*	Uganda	Low-Income	Eastern Africa	Single-Center	Kampala	Urban	July 2019 to March 2020	April 2020 to June 2020	"After the initial lockdown period (4 weeks without outpatient services), measures to reduce the number of women attending ANC included reducing the number of appointments per day from 150 to 90 for ANC and all women <26 weeks gestation being sent away to return after 30 weeks. For infants, the vaccination clinic remained operating routinely. During the initial phases of lockdown (April and May 2020), 35/60 doctors were reassigned to acute care at COVID-19 centres in anticipation of a large number of COVID-19 cases, but 53 nurses were recruited at the same time with result-based financing support raising the number of nurse/midwifes on site from 184 to 237 after April 2020."
4	Caniglia	*American Journal of Obstetrics & Gynecology*	Botswana	Middle-Income	Southern Africa	National	N/A	Not applicable/specified	April 3 to May 7, 2017-2019	April 3 to May 7, 2020	"Despite having only 3 re- ported SARS-CoV-2 cases at the time,9 Botswana announced a state of emer- gency because of COVID-19 on March 31, 2020,10 and a nationwide lockdown started at midnight on April 2, 2020.11e13 After the initial 28-day period, the lockdown was extended un- til May 7, 2020.14 Movement restrictions were gradually lifted between May 8, 2020, and May 22, 2020.15e19"

Supplemental Figure 4.2. Risk of bias assessment according to ROBINS-I

Risk of bias domains

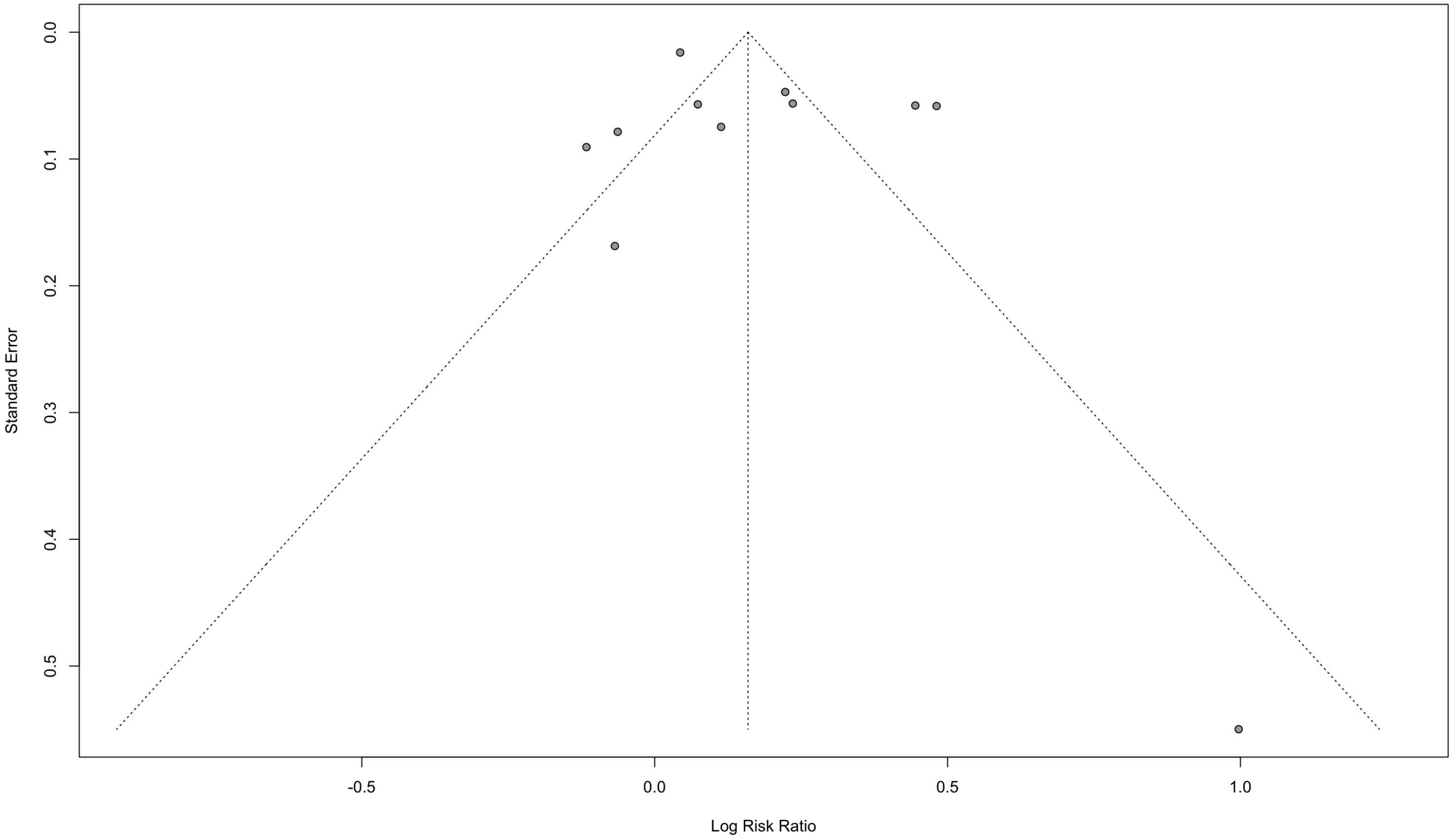
Study	D1	D2	D3	D4	D5	D6	D7	Overall
Abdul-Mumin	-	+	+	+	-	+	-	-
Arena	-	+	+	+	+	+	+	-
Bikwa	-	+	+	+	-	+	+	-
Burt	X	+	+	+	?	X	+	X
Caniglia	+	+	+	+	?	+	+	+
Carter	X	-	+	+	?	X	+	X
Chimhuya	-	+	+	+	+	+	+	-
Desta	-	+	+	+	?	+	-	-
Ezenwa	-	+	+	+	?	+	-	-
Farley	X	X	-	+	+	!	+	!
Kassie	-	+	+	+	?	+	+	-
Lydon	-	+	+	+	-	+	+	-
Naqvi	+	+	+	+	+	+	+	+
Okeke	-	-	+	+	+	-	+	-
Shakespeare	X	+	+	+	?	-	+	X
Shikuku	-	+	+	+	?	+	-	-

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
! Critical
X Serious
- Moderate
\+ Low
? No information

ROBINS-I = Risk Of Bias In Non-randomized Studies - of Interventions. Generated using Risk-of-bias VISualization (robvis).[69]

Supplemental Figure 4.3. Funnel plot for studies reporting on stillbirth



4.8. References

1. Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health*. 2021;9(6):e759-e772. doi:10.1016/S2214-109X(21)00079-6

2. Vaccaro C, Mahmoud F, Aboulatta L, Aloud B, Eltonsy S. The impact of COVID-19 first wave national lockdowns on perinatal outcomes: a rapid review and meta-analysis. *BMC Pregnancy Childbirth*. 2021;21(1):676. doi:10.1186/s12884-021-04156-y

3. Yao XD, Zhu LJ, Yin J, Wen J. Impacts of COVID-19 pandemic on preterm birth: a systematic review and meta-analysis. *Public Health*. 2022;213:127-134. doi:10.1016/j.puhe.2022.10.015

4. Hawco S, Rolnik DL, Woolner A, et al. The impact of mitigation measures on perinatal outcomes during the first nine months of the COVID-19 pandemic: A systematic review with meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2022;274:117-127. doi:10.1016/j.ejogrb.2022.05.007

5. Yang J, D’Souza R, Kharrat A, Fell DB, Snelgrove JW, Shah PS. COVID-19 pandemic and population-level pregnancy and neonatal outcomes in general population: A living systematic review and meta-analysis (Update#2: November 20, 2021). *Acta Obstet Gynecol Scand*. 2022;101(3):273-292. doi:10.1111/aogs.14318

6. Gajbhiye RK, Sawant MS, Kuppusamy P, et al. Differential impact of COVID-19 in pregnant women from high-income countries and low- to middle-income countries: A systematic review and meta-analysis. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet*. 2021;155(1):48-56. doi:10.1002/ijgo.13793

7. Calvert C, Brockway M (Merilee), Zoega H, et al. Changes in preterm birth and stillbirth during COVID-19 lockdowns in 26 countries. *Nat Hum Behav*. Published online February 27, 2023:1-16. doi:10.1038/s41562-023-01522-y

8. Caniglia EC, Magosi LE, Zash R, et al. Modest reduction in adverse birth outcomes following the COVID-19 lockdown. *Am J Obstet Gynecol*. 2021;224(6):615.e1-615.e12. doi:10.1016/j.ajog.2020.12.1198

9. Kassie A, Wale A, Yismaw W. Impact of Coronavirus Diseases-2019 (COVID-19) on Utilization and Outcome of Reproductive, Maternal, and Newborn Health Services at Governmental Health Facilities in South West Ethiopia, 2020: Comparative Cross-Sectional Study. *Int J Womens Health*. 2021;13:479-488. doi:10.2147/IJWH.S309096

10. Shakespeare C, Dube H, Moyo S, Ngwenya S. Resilience and vulnerability of maternity services in Zimbabwe: a comparative analysis of the effect of Covid-19 and lockdown control measures on maternal and perinatal outcomes, a single-centre cross-sectional study at Mpilo Central Hospital. *BMC Pregnancy Childbirth*. 2021;21(1):416. doi:10.1186/s12884-021-03884-5

11. World Health Organization. Democratic Republic of the Congo: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data. Accessed March 16, 2023. https://covid19.who.int

12. World Health Organization. Global: WHO Coronavirus (COVID-19) Dashboard. Accessed March 16, 2023. https://covid19.who.int

13. Nkuba AN, Makiala SM, Guichet E, et al. High Prevalence of Anti–Severe Acute Respiratory Syndrome Coronavirus 2 (Anti–SARS-CoV-2) Antibodies After the First Wave of Coronavirus Disease 2019 (COVID-19) in Kinshasa, Democratic Republic of the Congo: Results of a Cross-sectional Household-Based Survey. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021;74(5):882-890. doi:10.1093/cid/ciab515

14. Kogan NE, Gantt S, Swerdlow D, et al. Leveraging Serosurveillance and Postmortem Surveillance to Quantify the Impact of Coronavirus Disease 2019 in Africa. *Clin Infect Dis*. 2023;76(3):424-432. doi:10.1093/cid/ciac797

15. Hagan JE, Ahinkorah BO, Seidu AA, Ameyaw EK, Schack T. Africa's COVID-19 Situation in Focus and Recent Happenings: A Mini Review. *Front Public Health*. 2020;8:573636. doi:10.3389/fpubh.2020.573636

16. Tessema SK, Nkengasong JN. Understanding COVID-19 in Africa. *Nat Rev Immunol*. 2021;21(8):469-470. doi:10.1038/s41577-021-00579-y

17. Gilbert M, Pullano G, Pinotti F, et al. Preparedness and vulnerability of African countries against importations of COVID-19: a modelling study. *The Lancet*. 2020;395(10227):871-877. doi:10.1016/S0140-6736(20)30411-6

18. Ogunleye OO, Basu D, Mueller D, et al. Response to the Novel Corona Virus (COVID-19) Pandemic Across Africa: Successes, Challenges, and Implications for the Future. *Front Pharmacol*. 2020;11:1205. doi:10.3389/fphar.2020.01205

19. Adams J, MacKenzie MJ, Amegah AK, et al. The Conundrum of Low COVID-19 Mortality Burden in sub-Saharan Africa: Myth or Reality? *Glob Health Sci Pract*. 2021;9(3):433-443. doi:10.9745/GHSP-D-21-00172

20. Musa HH, Musa TH, Musa IH, Musa IH, Ranciaro A, Campbell MC. Addressing Africa's pandemic puzzle: Perspectives on COVID-19 transmission and mortality in sub-Saharan Africa. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. 2021;102:483-488. doi:10.1016/j.ijid.2020.09.1456

21. Njenga MK, Dawa J, Nanyingi M, et al. Why is There Low Morbidity and Mortality of COVID-19 in Africa? *Am J Trop Med Hyg*. 2020;103(2):564-569. doi:10.4269/ajtmh.20-0474

22. World Health Organization. HIV/AIDS. WHO | Regional Office for Africa. Accessed April 20, 2023. https://www.afro.who.int/health-topics/hivaids

23. Hug L, You D, Blencowe H, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. *The Lancet*. 2021;398(10302):772-785. doi:10.1016/S0140-6736(21)01112-0

24. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0

25. Blencowe H, Krasevec J, Onis M de, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. 2019;7(7):e849-e860. doi:10.1016/S2214-109X(18)30565-5

26. Kebede D, Zielinski C, Mbondji PE, Piexoto M, Kouvividila W, Lusamba-Dikassa PS. The way forward – narrowing the knowledge gap in sub-Saharan Africa to strengthen health systems. *J R Soc Med*. 2014;107(1 Suppl):10-12. doi:10.1177/0141076813512818

27. African Union. Member States | African Union. Accessed February 8, 2022. https://au.int/en/member_states/countryprofiles2

28. Hale T, Angrist N, Goldszmidt R, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nat Hum Behav*. 2021;5(4):529-538. doi:10.1038/s41562-021-01079-8

29. Mathieu E, Ritchie H, Rodés-Guirao L, et al. Coronavirus Pandemic (COVID-19). *Our World Data*. Published online March 5, 2020. Accessed April 20, 2023. https://ourworldindata.org/covid-stringency-index

30. World Health Organization. Low birth weight. Accessed January 31, 2022. https://www.who.int/data/maternal-newborn-child-adolescent-ageing/advisory-groups/gama/gama-related-resources/nlis

31. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club*. 1995;123(3):A12-13.

32. Eriksen MB, Frandsen TF. The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. *J Med Libr Assoc JMLA*. 2018;106(4):420-431. doi:10.5195/jmla.2018.345

33. Zotero. Zotero | Your personal research assistant. Accessed April 21, 2023. https://www.zotero.org/

34. Arena PJ. *Chapter 3. The Impact of COVID-19 Mitigation Measures on Neonatal Health Outcomes in Kinshasa, Democratic Republic of the Congo: An Interrupted Time Series Analysis | The Impact of the COVID-19 Pandemic on Neonatal Health Outcomes in Sub-Saharan Africa: A Targeted Investigation of Medical Records in Kinshasa, Democratic Republic of the Congo with an Expansive Meta-Analysis among Sub-Saharan Countries*. University of California, Los Angeles; Unpublished.

35. Egger M, Smith GD. Principles of and Procedures for Systematic Reviews. In: *Systematic Reviews in Health Care*. John Wiley & Sons, Ltd; 2001:23-42. doi:10.1002/9780470693926.ch2

36. World Bank. World Bank Country and Lending Groups – World Bank Data Help Desk. World Bank Data. Accessed April 24, 2023. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

37. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi:10.1136/bmj.i4919

38. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009;2009(1):MR000006. doi:10.1002/14651858.MR000006.pub3

39. Sterne JAC, Egger M, Smith GD. Investigating and Dealing with Publication and Other Biases. In: *Systematic Reviews in Health Care*. John Wiley & Sons, Ltd; 2001:189-208. doi:10.1002/9780470693926.ch11

40. Lin L, Chu H. Quantifying Publication Bias in Meta-Analysis. *Biometrics*. 2018;74(3):785-794. doi:10.1111/biom.12817

41. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.

42. Deeks JJ, Altman DG, Bradburn MJ. Statistical Methods for Examining Heterogeneity and Combining Results from Several Studies in Meta-Analysis. In: *Systematic Reviews in Health Care*. John Wiley & Sons, Ltd; 2001:285-312. doi:10.1002/9780470693926.ch15

43. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1(2):97-111. doi:10.1002/jrsm.12

44. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153-160. doi:10.1136/ebmental-2019-300117

45. PROSPERO. International prospective register of systematic reviews (PROSPERO). About PROSPERO | What is registration? Accessed April 20, 2023. https://www.crd.york.ac.uk/prospero/#aboutpage

46. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi:10.1136/bmj.b2700

47. Lydon MM, Vilanculos J, Martinez A, Barata A, Keyes E. Effects of the COVID-19 pandemic on maternal and perinatal health service utilisation and outcomes in Mozambique:

an interrupted time series analysis. *BMJ Open*. 2022;12(11):e062975. doi:10.1136/bmjopen-2022-062975

48. Chimhuya S, Neal SR, Chimhini G, et al. Indirect impacts of the COVID-19 pandemic at two tertiary neonatal units in Zimbabwe and Malawi: an interrupted time series analysis. *BMJ Open*. 2022;12(6):e048955. doi:10.1136/bmjopen-2021-048955

49. Egger M, Smith GD, Schneider M. Systematic Reviews of Observational Studies. In: *Systematic Reviews in Health Care*. John Wiley & Sons, Ltd; 2001:211-227. doi:10.1002/9780470693926.ch12

50. Justman N, Shahak G, Gutzeit O, et al. Lockdown with a Price: The impact of the COVID-19 Pandemic on Prenatal Care and Perinatal Outcomes in a Tertiary Care Center. *Isr Med Assoc J IMAJ*. 2020;22(9):533-537.

51. Ezenwa BN, Fajolu IB, Nabwera H, Wang D, Ezeaka CV, Allen S. Impact of COVID-19 lockdown measures on institutional delivery, neonatal admissions and prematurity: a reflection from Lagos, Nigeria. *BMJ Paediatr Open*. 2021;5(1):e001029. doi:10.1136/bmjpo-2021-001029

52. Naqvi S, Naqvi F, Saleem S, et al. Health Care in Pregnancy During the COVID-19 Pandemic and Pregnancy Outcomes in Six Low-and-Middle-Income Countries: Evidence from a Prospective, Observational Registry of the Global Network for Women's and Children's Health. *BJOG Int J Obstet Gynaecol*. Published online April 4, 2022. doi:10.1111/1471-0528.17175

53. DHIS2. About DHIS2. DHIS2. Accessed October 28, 2021. https://dhis2.org/about/

54. Dehnavieh R, Haghdoost A, Khosravi A, et al. The District Health Information System (DHIS2): A literature review and meta-synthesis of its strengths and operational challenges based on the experiences of 11 countries. *Health Inf Manag J*. 2019;48(2):62-75. doi:10.1177/1833358318777713

55. Egger M, Smith GD, O'Rourke K. Introduction: Rationale, Potentials, and Promise of Systematic Reviews. In: *Systematic Reviews in Health Care*. John Wiley & Sons, Ltd; 2001:1-19. doi:10.1002/9780470693926.ch1

56. Fagard RH, Staessen JA, Thijs L. Advantages and disadvantages of the meta-analysis approach. *J Hypertens Suppl Off J Int Soc Hypertens*. 1996;14(2):S9-12; discussion S13. doi:10.1097/00004872-199609002-00004

57. Egger M, Dickersin K, Smith GD. Problems and Limitations in Conducting Systematic Reviews. In: *Systematic Reviews in Health Care*. John Wiley & Sons, Ltd; 2001:43-68. doi:10.1002/9780470693926.ch3

58. Burt JF, Ouma J, Lubyayi L, et al. Indirect effects of COVID-19 on maternal, neonatal, child, sexual and reproductive health services in Kampala, Uganda. *BMJ Glob Health*. 2021;6(8). doi:10.1136/bmjgh-2021-006102

59. Okeke EN, Abubakar IS, De Guttry R. In Nigeria, Stillbirths And Newborn Deaths Increased During The COVID-19 Pandemic. *Health Aff Proj Hope*. 2021;40(11):1797-1805. doi:10.1377/hlthaff.2021.00659

60. Reade MC, Delaney A, Bailey MJ, Angus DC. Bench-to-bedside review: Avoiding pitfalls in critical care meta-analysis – funnel plots, risk estimates, types of heterogeneity, baseline risk and the ecologic fallacy. *Crit Care*. 2008;12(4):220. doi:10.1186/cc6941

61. Geissbühler M, Hincapié CA, Aghlmandi S, Zwahlen M, Jüni P, da Costa BR. Most published meta-regression analyses based on aggregate data suffer from methodological pitfalls: a meta-epidemiological study. *BMC Med Res Methodol*. 2021;21(1):123. doi:10.1186/s12874-021-01310-0

62. Abdul-Mumin A, Cotache-Condor C, Bimpong KA, et al. Decrease in Admissions and Change in the Diagnostic Landscape in a Newborn Care Unit in Northern Ghana During the COVID-19 Pandemic. *Front Pediatr*. 2021;9:642508. doi:10.3389/fped.2021.642508

63. Bikwa Y, Murewanhema G, Kanyangarara M, Madziyire MG, Chirenje ZM. Impact of COVID-19 on maternal and perinatal outcomes in Harare, Zimbabwe: a comparative maternal audit. *J Glob Health Rep*. 2021;5:e2021093. doi:10.29392/001c.28995

64. Carter ED, Zimmerman L, Qian J, Roberton T, Seme A, Shiferaw S. Impact of the Early Stages of the COVID-19 Pandemic on Coverage of Reproductive, Maternal, and Newborn Health Interventions in Ethiopia: A Natural Experiment. *Front Public Health*. 2022;10:778413. doi:10.3389/fpubh.2022.778413

65. Desta AA, Woldearegay TW, Gebremeskel E, et al. Impacts of COVID-19 on essential health services in Tigray, Northern Ethiopia: A pre-post study. *PloS One*. 2021;16(8):e0256330. doi:10.1371/journal.pone.0256330

66. Farley E, Edwards A, Numanoglu E, Phillips TK. Lockdown babies: Birth and new parenting experiences during the 2020 Covid-19 lockdown in South Africa, a cross-sectional study. *Women Birth J Aust Coll Midwives*. Published online September 8, 2021:S1871-5192(21)00152-9. doi:10.1016/j.wombi.2021.09.001

67. Shikuku DN, Nyaoke IK, Nyaga LN, Ameh CA. Early indirect impact of COVID-19 pandemic on utilisation and outcomes of reproductive, maternal, newborn, child and adolescent health services in Kenya: A cross-sectional study. *Afr J Reprod Health*. 2021;25(6). Accessed April 25, 2023. https://www.ajrh.info/index.php/ajrh/article/view/3035

68. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

69. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2020;n/a(n/a). doi:10.1002/jrsm.1411

Chapter 5. Concluding Remarks

5.1. Outcomes and Implications

Despite its importance as a vital pillar within public health that supports not only the short- and long-term health but also the socioeconomic development of communities and countries, maternal and neonatal health can sometimes be overlooked. Global health programs, like the Every Newborn Action Plan,[1–3] and novel interventions, such as maternal immunization,[4–7] are therefore key strategies for promoting maternal and neonatal health and thus improving overall population health. However, surveillance system challenges exist in low- and middle-income countries (LMICs) that hinder the abilities of these programs and interventions to be fully effective; furthermore, the unprecedented nature of the COVID-19 pandemic resulted in additional burden on already struggling public health systems in LMICs, thereby leading to more population health challenges. Thus, more research on surveillance systems – including pharmacovigilance (PV) systems – strengthening as well as the impact of the COVID-19 pandemic within LMICs is clearly needed.

This dissertation sought to identify solutions for PV systems strengthening for the benefit of maternal and neonatal health outcomes and to examine the impact of the COVID-19 pandemic on neonatal health outcomes within the context of the Democratic Republic of the Congo (DRC) specifically and sub-Saharan Africa more generally. In general, we found that alternative data sources in the form of archival medical records and enhanced monitoring data could serve as suitable tools for the monitoring of adverse birth outcomes in Kinshasa, DRC; additionally, our natural experimental analyses revealed that low birth weight (LBW) and preterm birth (PTB) slightly decreased after the imposition of COVID-19 mitigation measures in Kinshasa, DRC, while our systematic review and meta-analysis suggested no change in stillbirth, LBW, or PTB after the imposition of COVID-19 mitigation measures among multi-national/national/regional studies in sub-Saharan Africa. Despite limitations associated with the data and our analytical choices, the key findings of this dissertation and the corresponding implications for future research and public health are as follows:

1. Archival medical records and enhanced monitoring data can be validly used as alternative – and perhaps superior – PV tools for the surveillance of maternal and neonatal health outcomes in Kinshasa, DRC; indeed, comparisons with the literature[8–10] suggested these alternative data sources may have in fact better recorded PTB prevalence than the standard surveillance data source in the DRC. However, there were challenges related to the measurement of maternal age, likely due to the moderate missingness observed in both the archival medical records and the enhanced surveillance data. Nonetheless, our results have implications for the Congolese PV infrastructure and provide evidence in favor of utilizing archival medical records/enhanced monitoring data (in conjunction with spontaneous reporting mechanisms and standard surveillance) to address vaccine/drug safety inquiries more effectively in Kinshasa. Future work should aim to capture maternal age information more accurately, especially in the archival medical records.
2. Despite some issues in our ability to definitively assess the seasonality of the adverse birth outcomes, we determined that the stillbirth rate appeared to not increase while the LBW and PTB rates seemed to decline slightly after the imposition of COVID-19 mitigation measures in Kinshasa, DRC. Our results thus provide key insights for both Congolese and global health policymakers regarding the impact of COVID-19 mitigation measures on neonatal health outcomes in the DRC. Additionally, our findings have significant implications for public health responses to potential future outbreaks of other infectious

diseases in the DRC (such as cholera, measles, malaria, and Ebola virus disease)[11,12] that may require the introduction of similar mitigation measures in Kinshasa. Future research should aim to better understand the seasonality of the adverse birth outcomes and to investigate the impact of the COVID-19 pandemic on neonatal health outcomes in other parts of the country in order to provide a more comprehensive understanding within the DRC.

3. Our systematic review and meta-analysis suggested that the risk of stillbirth and LBW potentially increased during the imposition of COVID-19 mitigation measures, while the risk of PTB did not change during such periods; however, there were significant differences by study design. More specifically, multi-national/national/regional studies indicated that there was no change in the risk of stillbirth or LBW during COVID-19 mitigation measures, while multi-/single-center investigations indicated that there was an increase in both outcomes during such periods. As proposed by other researchers,[13–15] facility-specific challenges and/or shifts in pregnancy may drive any changes detected in multi-/single-center investigations; thus, such results should be interpreted with caution, thereby suggesting that the results from the multi-national/national/regional studies should be prioritized. Moreover, due to issues surrounding high heterogeneity and a small number of studies/countries included for our analyses, future research should aim to conduct more national/regional studies within more sub-Saharan African countries in order to further elucidate the impact of pandemic policies on neonatal health outcomes in the region.

5.2. Conclusion

Although it could be argued that PV capabilities in the DRC and the COVID-19 pandemic's association with neonatal health outcomes both within the DRC and throughout sub-

Saharan Africa are not necessarily related topics, this dissertation succeeded in addressing these subjects and providing novel contributions to the literature. As the PV infrastructure in the DRC continues to develop, we hope that Congolese researchers can use the information generated in Chapter 2 to help expand the capabilities of the national PV system. Likewise, we anticipate that the results from Chapter 3 and Chapter 4 can facilitate further global dialogue on the impact of the COVID-19 pandemic on neonatal health outcomes and spur continued research in this area so that a more complete picture of the impact of COVID-19 mitigation measures in sub-Saharan Africa can be formed. Ultimately though, it is our desire that the findings generated from this dissertation can be used to promote maternal and neonatal health and thus improve overall population health both within the DRC and across the globe.

5.3. References

1. World Health Organization. Newborns: improving survival and well-being. Published September 19, 2020. Accessed May 2, 2023. https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality

2. World Health Organization. Every Newborn Action Plan. Accessed May 2, 2023. https://www.who.int/initiatives/every-newborn-action-plan

3. World Health Organization, United Nations Children's Fund (UNICEF). *Every Newborn Progress Report 2019*.; 2020. Accessed May 2, 2023. https://www.healthynewbornnetwork.org/resource/every-newborn-progress-report-2019-2/

4. Omer SB. Maternal Immunization. *N Engl J Med*. 2017;376(13):1256-1267. doi:10.1056/nejmra1509044

5. Engmann C, Fleming JA, Khan S, et al. Closer and closer? Maternal immunization: current promise, future horizons. *J Perinatol*. 2020;40(6):844-857. doi:10.1038/s41372-020-0668-3

6. World Health Organization. *Maternal Immunization and Antenatal Care Service Delivery Situation Analysis: Report of the MIACSA Project, 2016-2019*. World Health Organization; 2020. https://www.who.int/publications/i/item/9789240004016

7. Niewiesk S. Maternal Antibodies: Clinical Significance, Mechanism of Interference with Immune Responses, and Possible Vaccination Strategies. *Front Immunol*. 2014;5. Accessed May 2, 2023. https://www.frontiersin.org/articles/10.3389/fimmu.2014.00446

8. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0

9. Cao G, Liu J, Liu M. Global, Regional, and National Incidence and Mortality of Neonatal Preterm Birth, 1990-2019. *JAMA Pediatr*. 2022;176(8):787-796. doi:10.1001/jamapediatrics.2022.1622

10. Kasonia K. Safety of the Ad26.Zebov, MVA-BN-Filo Ebola virus vaccine in pregnant women in an open-label clinical trial conducted during the 2018-2020 Ebola virus outbreak in the Democratic Republic of the Congo. Presented at: 2022 Annual Meeting of the American Society of Tropical Medicine & Hygiene; October 31, 2022; Seattle, USA.

11. Arie S. Congo sees rise in deaths from malaria, measles, and cholera as Ebola outbreak swallows up resources. *BMJ*. 2019;366:l4522. doi:10.1136/bmj.l4522

12. Nachega JB, Mbala-Kingebeni P, Otshudiema J, Zumla A, Tam-Fum JJM. The colliding epidemics of COVID-19, Ebola, and measles in the Democratic Republic of the Congo. *Lancet Glob Health*. 2020;8(8):e991-e992. doi:10.1016/S2214-109X(20)30281-3

13. Yang J, D'Souza R, Kharrat A, Fell DB, Snelgrove JW, Shah PS. COVID-19 pandemic and population-level pregnancy and neonatal outcomes in general population: A living systematic review and meta-analysis (Update#2: November 20, 2021). *Acta Obstet Gynecol Scand*. 2022;101(3):273-292. doi:10.1111/aogs.14318

14. Justman N, Shahak G, Gutzeit O, et al. Lockdown with a Price: The impact of the COVID-19 Pandemic on Prenatal Care and Perinatal Outcomes in a Tertiary Care Center. *Isr Med Assoc J IMAJ*. 2020;22(9):533-537.

15. Calvert C, Brockway M (Merilee), Zoega H, et al. Changes in preterm birth and stillbirth during COVID-19 lockdowns in 26 countries. *Nat Hum Behav*. Published online February 27, 2023:1-16. doi:10.1038/s41562-023-01522-y