Title:

SARS-CoV-2 Infection and Pregnancy in sub-Saharan Africa: A Six-Country Retrospective Cohort Analysis

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ABSTRACT

Background: Little data is available about COVID-19 outcomes among pregnant women in sub-Saharan Africa (SSA), where high-risk comorbidities are prevalent. We investigated the impact of pregnancy on SARS-CoV-2 infection and of SARS-CoV-2 infection on pregnancy to generate evidence for health policy and clinical practice.

Methods: We conducted a six-country retrospective cohort study among hospitalized women of childbearing age between March 1, 2020 and March 31, 2021. Exposures were 1) pregnancy and 2) a positive SARS-CoV-2 RT-PCR test. The primary outcome for both analyses was intensive care unit (ICU) admission. Secondary outcomes included supplemental oxygen requirement, mechanical ventilation, adverse birth outcomes, and in-hospital mortality. We used log-binomial regression to estimate the effect between pregnancy and SARS-CoV-2 infection. Factors associated with mortality were evaluated using competing-risk proportional sub-distribution hazards models.

Results: Our analyses included 1,315 hospitalized women: 510 pregnant women with SARS-CoV-2; 403 non-pregnant women with SARS-CoV-2, and 402 pregnant women without SARS-CoV-2 infection. Among women with SARS-CoV-2 infection, pregnancy was associated with increased risk for ICU admission (adjusted risk ratio [aRR]=2.38, 95%CI:1.42–4.01), oxygen supplementation (aRR=1.86, 95%CI:1.44–2.42) and hazard of in-hospital death (adjusted sub-hazard ratio [aSHR]=2.00; 95%CI: 1.08–3.70). Among pregnant women, SARS-CoV-2 infection increased the risk of ICU admission (aRR=2.0, 95%CI:1.20–3.35), oxygen supplementation (aRR=1.57, 95%CI:1.17–2.11), and hazard of in-hospital death (aSHR=5.03;95%CI:1.79–14.13).

Conclusions: Among hospitalized women in SSA, both SARS-CoV-2 infection and pregnancy independently increased risks of ICU admission, oxygen supplementation, and death. These data support international recommendations to prioritize COVID-19 vaccination among pregnant women.

40-WORD SUMMARY

In hospitalized African women, both SARS-CoV-2 infection and pregnancy independently increased risks of morbidity and mortality. In addition, among pregnant and non-pregnant women with SARS-CoV-2 infection, HIV, prior TB, sickle cell anemia, and nongestational diabetes increased risk of ICU admission.

INTRODUCTION

Few studies have been published on the impact of SARS-CoV-2 infection on pregnancy in sub-Saharan Africa (SSA). Poor maternal and child health outcomes coupled with a high prevalence of communicable and noncommunicable diseases necessitate investigation of the impact of SARS-CoV-2 in these settings [1]. Reports from mostly outside SSA suggest that SARS-CoV-2 infection in pregnant women is associated with increased risk for intensive care unit (ICU) admission, invasive ventilation, and death when compared to similar-age, non-pregnant women with SARS-CoV-2 infection [2-6]. The multinational INTERCOVID cohort study determined that SARS-CoV-2 infection in pregnancy was associated with increased maternal and neonatal morbidity and mortality, when pregnant women with (N=706) and without (N=1,424) SARS-CoV-2 infection were compared [7]. However, it included only two (West) African countries (Ghana and Nigeria), representing 5% of the cohort. Consequently, INTERCOVID was not powered to assess outcomes across SSA and did not include a control group of non-pregnant women with SARS-CoV-2 infection.

The African Forum for Research and Education in Health (AFREhealth) COVID-19 Research Collaboration is a multi-disciplinary, pan-African consortium addressing maternal and child health issues relevant to SARS-CoV-2 [1,8,9]. Routine data collected as part of institutional and national COVID-19 responses are pooled from multiple countries and analysed to inform health policy and clinical practice in SSA, where co-morbidities such as HIV, tuberculosis (TB), and malaria are highly prevalent and access to/availability of COVID-19 prevention and treatment is low [1,10-12]. Here, we aimed to investigate the impact of pregnancy on SARS-CoV-2 infection and of SARS-CoV-2 infection on pregnancy in SSA and to provide evidence for vaccination and other prevention and treatment policy recommendations.

METHODS

Study Design, Participants, and Settings

We conducted a retrospective cohort study comparing clinical outcomes among three cohorts: 1) hospitalized pregnant women with RT-PCR-confirmed SARS-CoV-2 infection; 2) hospitalized non-pregnant women with RT-PCR-confirmed SARS-CoV-2 infection; and 3) hospitalized pregnant women without RT-PCR-confirmed SARS-CoV-2 infection and admitted for other obstetrical or medical reasons. We pooled all available routinely collected COVID-19 data from women of childbearing age hospitalized between March 1, 2020 and March 31, 2021 from 22 sites in 6 SSA countries: the Democratic Republic of Congo, Ghana, Kenya, Nigeria, South Africa, and Uganda. Detailed information about sample size and power, participating sites, regulatory approvals, SARS-CoV-2 RT-PCR testing platforms, and STROBE checklist [13] is available in **e-Tables 1, 2, 3, 4, 5 and e-Figures 3, 4.**

Variables

The World Health Organization (WHO) COVID-19 pregnancy case report form was used to extract demographic and clinical data from national or institutional COVID-19 datasets and/or hospital charts/registers [14]. Data collected included age and pregnancy status; signs, symptoms and WHO COVID-19 stage at admission; HIV serostatus; TB (active and past); malaria; noncommunicable disease comorbidities; general clinical outcomes; and pregnancy-specific outcomes, including miscarriage (<28 weeks' gestation), stillbirth (>28 weeks' gestation), prematurity (<37 weeks), low infant birth weight (<2,500 grams), and mode of delivery (vaginal or caesarean). For missing data on pre-existing comorbidities, we conservatively assumed that the specific comorbidity was absent, to minimize bias.

Statistical analysis

The two exposures of interest for the analyses (SARS-CoV-2 effect on pregnancy and vice versa) were 1) documented pregnancy and 2) a positive SARS-CoV-2 RT-PCR test. The primary outcome was ICU admission. Secondary outcomes included supplemental oxygen, mechanical ventilation, pregnancy/birth outcomes, and maternal/perinatal in-hospital mortality. All analyses were performed using STATA software version 16.1 (StataCorp, College Station, TX, USA).

Comparison of COVID-19 outcomes by pregnancy status

We summarized baseline demographic and clinical characteristics using frequencies and proportions stratified by pregnancy status (pregnant or non-pregnant). Risk ratios and associated 95% confidence intervals (CIs) estimated by log-binomial regression models were used to measure the strength of association between pregnancy and outcomes. Demographic and comorbidity variables associated with each outcome were explored using bivariable log-binomial regression models, and those with p-values <0.10 were included in multivariable regression models to identify potential confounders. To further explore the effect of confounding on our estimates of pregnancy effect on each outcome, an inverse probability-of-participation-based weighting (IPPW) regression approach was also used to adjust our analysis for baseline disparities. To estimate the weights, we first fitted a logistic regression model of “pregnant” versus “not pregnant” as a function of baseline characteristics hypothesized as potential confounders, including age, region, diabetes mellitus, HIV status, and history of TB. For each patient, we then estimated the probability of pregnancy from the fitted model based on her characteristics. Finally, we estimated the statistical weight for each patient as the inverse of her estimated probability of being pregnant if the patient was pregnant, or the inverse of the probability of non-pregnancy if the patient was not pregnant.

Time-to-death was evaluated by competing risk analysis using cumulative incidence function, with patient's hospital transfer as a competing event and hospital discharge as a censoring event. Factors associated with in-hospital mortality were estimated using Fine and Gray's proportional sub-distribution hazards model [15]. We used a multivariable proportional sub-distribution hazards model to estimate the adjusted sub-distribution hazard ratios (aSHRs) and associated 95% CIs. We assessed the proportionality of sub-hazards assumption by including time interactions on covariates in the model. Significant time-covariate interactions indicate violation of the proportionality assumption. Furthermore, we examined interactions to assess whether a synergistic effect existed between pregnancy and HIV or TB for risk of ICU admission or death among SARS-CoV-2-infected women

Comparison of pregnancy outcomes by SARS-CoV-2 RT-PCR result status

We summarized baseline demographic and clinical characteristics using frequencies and proportions stratified by SARS-CoV-2 RT-PCR result status. A complete case analysis approach was used for the primary and secondary outcomes, since the proportion of missing primary outcomes data was low (<4%).

RESULTS

As shown on the patient flow diagrams (**e-Figure 1, Panels A, B, C)** and **Table 1**, we analyzed data from 1,315 women in 6 SSA countries, including 510 pregnant women with SARS-CoV-2 infection, 403 non-pregnant women with SARS-CoV-2 infection, and 402 pregnant women without SARS-CoV-2 infection.

Comparison of SARS-CoV-2-infected women by pregnancy status

Demographics and Clinical Characteristics at admission

Pregnant women were younger than non-pregnant women, with median age of 30 years in both pregnant SARS-CoV-2-infected and -uninfected women versus 33 years in non-pregnant, SARS-CoV-2-infected women (**Table 1**). The geographic distribution of 913 women with RT-PCR-confirmed SARS-CoV-2 infection was 271 (30%), 67 (7%), 229 (25%), and 346 (38%) from East, West, Central, and Southern Africa regions, respectively. Most pregnant women (46%) with SARS-CoV-2 were from Southern Africa, whereas most (37.2%) non-pregnant women with SARS-CoV-2 were from Central Africa. Most (71.5%) pregnant women with SARS-CoV-2 and known gestational age at admission were in the third trimester (**Table 1**). At admission, among 913 SARS-CoV-2-infected women, 43.6% had mild, 12.4% moderate, 35.9% severe, and 8.1% critical COVID-19. Pregnant women were more likely to present with critical or severe disease than non-pregnant women (50% *vs*. 37%, respectively, p<0.001).

Signs, Symptoms, and Comorbidities

Several symptoms or comorbidities were more common in SARS-CoV-2-infected pregnant (vs. non-pregnant) women: cough (318/489, 65% *vs*. 229/396, 58%, p=0.028), history of previous TB (21/510, 4% *vs*. 6/403, 2%, p=0.02), HIV infection (107/510, 21% *vs*. 30/403, 7%, p<0.001), and acute malaria (15/510, 3% *vs.* 2/403, 1%, p=0.017). Non-pregnant women were more likely to have fever (145/391, 37% *vs*. 144/478, 30%, p=0.03), chest pain (70/239, 29% *vs*. 66/407, 16%, p<0.001), diarrhoea (23/248, 9% *vs*. 21/470, 4%, p=0.011), and a history of diabetes mellitus (39/403, 10% *vs*. 24/510, 5%, p=0.003). Regional comorbidity distribution is shown in **e-Table 6**.

Clinical Outcomes

Among 913 hospitalized women with SARS-CoV-2 infection, 1.3% had undocumented outcomes. Among 901 women with documented outcomes, 85.8% were discharged, 8.0% died, 3.6% were transferred to another facility, and 2.7% remained hospitalized at the end of data collection. Patient flow diagrams (**e-Figure 1, Panels A, B, C)** show the proportion of women who were admitted to an ICU, received supplemental oxygen or mechanical ventilation, or died, by pregnancy and SARS-CoV-2 infection status. **Figure 1** highlights key unadjusted findings: pregnant women with SARS-CoV-2 infection were significantly more likely than non-pregnant women with SARS-CoV-2 infection to be admitted to an ICU, require supplemental oxygen, and die in-hospital. ICU admission rates among women with SARS-CoV-2 infection varied by region: 22% in West Africa, 14% in Southern Africa, 11% in East Africa, and in 10% Central Africa. Regional differences in supplemental oxygen requirement, invasive ventilation, and mortality were also noted (**e-Figure 2**).

e-Table 7 shows the association between potential confounders and pregnancy before and after adjusting with IPPW. **Figure 2** shows the unadjusted (**Panel A**) and IPPW-adjusted (**Panel B**) comparison of outcomes between hospitalized pregnant and non-pregnant women with SARS-CoV-2 infection. Adjusting for differences in age, HIV status, diabetes, region, and history of previous TB, being pregnant was associated with a significantly higher risk of ICU admission (adjusted RR [aRR]= 2.38, 95% CI: 1.42–4.01). More pregnant than non-pregnant women received supplemental oxygen, adjusting for baseline differences (aRR=1.81, 95% CI: 1.30–2.50). Among SARS-CoV-2-infected women, 51 (10%) pregnant women died, compared to 21 (5%) non-pregnant women. In unadjusted analyses, pregnancy increased the risk of death by more than 90% (RR=1.94, 95% CI: 1.19–3.17). In IPPW-adjusted analyses, pregnancy remained marginally associated with a higher risk of mortality (aRR=1.66, 95% CI: 0.95–2.88).

Table 2 summarizes factors associated with ICU admission for all women with SARS-CoV-2 infection, after adjusting for pregnancy status and region. Living with HIV, history of previous TB, diabetes, and sickle cell disease were independently associated with higher risk of ICU admission. Adjusting for pregnancy status and region, women with multiple (>1) comorbidities had significantly higher risk of ICU admission vs. women without comorbidities. No synergistic interaction was observed between pregnancy and HIV or TB for risk of ICU admission or death among SARS-CoV-2-infected women.

e-Table 8 shows associations between demographic and clinical factors and the hazard of in-hospital mortality in all women with SARS-CoV-2 infection, using Fine and Gray's model. In this competing risk analysis, being pregnant was significantly associated with an increased hazard of in-hospital death (**Figure 3, Panel A**). Furthermore, adjusting for pregnancy status and region, chronic kidney disease, asthma, and diabetes were independently associated with risk of death. Women with multiple comorbidities were at increased risk of death compared to those without comorbidities (**Figure 3, Panel B**). Residing in Southern or West Africa was associated with higher risk of mortality compared to East African residence (**Figure 3, Panel C).**

Comparison of pregnant women by SARS-CoV-2 infection status

Demographics, Clinical Characteristics, and Mortality

We compared 510 SARS-CoV-2-infected pregnant women (**e-Figure 1, Panel A**) to 402 SARS-CoV-2-uninfected pregnant women (**e-Figure 1, Panel C**). There were no significant differences in demographic and clinical characteristics between SARS-CoV-2-infected and -uninfected pregnant women, except for regional residence, as shown in **Table 1**. **Figure 2** shows the unadjusted (**Panel C**) and IPPW-adjusted (**Panel D**) comparisons of ICU admission, need for supplemental oxygen, mechanical ventilation, and death between pregnant SARS-CoV-2-

infected and -uninfected women. SARS-CoV-2 infection increased the risk of ICU admission, receiving oxygen supplementation, and maternal death. In a competing risk analysis, SARS-CoV-2-infected (vs. uninfected) pregnant women had a five-times greater hazard of in-hospital death (**Figure 3, Panel D**).

Pregnancy and Perinatal Outcomes

Among 510 SARS-CoV-2-infected pregnant women, 32% had not delivered at the time of data collection and 19% had missing information; among 402 SARS-CoV-2-uninfected pregnant women, 5% had not delivered at the time of data collection and 9% had missing information. Among 250 SARS-CoV-2-infected pregnant women with documented pregnancy outcomes, 213 (85%) had live births and 37 (15%) experienced foetal loss [14 miscarriages, 2 induced abortion, and 21 stillbirths] **(e-Table 9)**. Among 345 SARS-CoV-2-uninfected pregnant women with documented pregnancy outcomes, 302 (88%) had live births and 43 (12%) experienced foetal loss [24 miscarriages, 2 induced abortion, and 17 stillbirths]. Caesarean delivery was more frequent among SARS-CoV-2-infected than -uninfected women (RR=1.56, 95% CI: 1.29–1.89), and the proportions of preterm (69/213, 32% vs. 94/302, 31% respectively, p=0.87) and low birth weight infants (72/213, 34%vs. 97/314, 31%, p=0.71) were similar. Early neonatal in-hospital death occurred among 4% and 3% infants of SARS-CoV-2-infected and -uninfected mothers, respectively (RR=1.46, 95% CI: 0.56–3.84).

DISCUSSION

In this large multi-country cohort analysis in SSA, we found that among women with SARS-CoV-2 infection, pregnancy independently increased the risk of in-hospital morbidity (ICU admission or supplemental oxygen requirement) and, in competing risk analyses, increased hazard of in-

hospital death. Among pregnant women, SARS-CoV-2 infection independently increased the risk of ICU admission, oxygen supplementation, and death. Furthermore, among all (pregnant and non-pregnant) women with SARS-CoV-2 infection, HIV infection, prior TB, sickle cell anemia, and non-gestational diabetes increased the risk of ICU admission.

Similar to our findings, the 18-country INTERCOVID study (including Ghana and Nigeria) reported higher risks of ICU admission and mortality among pregnant women with (N=706) vs. without (N=1,424) SARS-CoV-2 infection [7]. However, unlike our study, INTERCOVID included non-hospitalized asymptomatic women and did not include non-pregnant women with SARS-CoV-2 infection. Analysis of two smaller cohorts of SARS-CoV-2-positive pregnant women from DR Congo (N=12) and Ethiopia (N=27) did not find associations between pregnancy and adverse outcomes, likely due to small numbers and/or lack of control groups [17,18], and an initial US retrospective cohort study found pregnancy associated with higher morbidity but not mortality [16]. In contrast, in a U.S. Centers for Disease Control and Prevention report on a larger cohort of women (23,434 pregnant and 386,028 non-pregnant) with SARS-CoV-2 infection, pregnancy was associated with a 1.7 times (95% CI 1.2-2.4) increased risk of mortality in adjusted analyses [2]. Similarly, a Mexican study including more than 260,000 SARS-CoV-2-infected women found that pregnancy increased the risk of death among women aged 15 to 44 years by 61% [19]. These large studies corroborate our findings: in an adjusted competing-risk analysis, pregnancy increased hazard of maternal death two-fold among SARS-CoV-2-infected women.

Pregnant and non-pregnant women with SARS-CoV-2 infection who were living with HIV or had prior history of TB had a nearly two-fold increased risk of ICU admission compared to those without these chronic infections. Published data on the impact of HIV on SARS-CoV-2 infection outcomes have been conflicting [6, 20, 21]. However, a recent data analysis by the WHO found that HIV in hospitalized adults was independently associated with a 1.29 times higher risk of death

from SARS-CoV-2 infection after adjusting for age, sex, and underlying conditions [22]. Our finding of an association between prior TB and COVID-19 severity may reflect decreased pulmonary reserve due to post-TB sequelae, as described by Tadolini et al. [23]. The finding of higher rates of acute malaria in pregnant vs. non-pregnant women with SARS-CoV-2 infection was expected, as pregnant women are more susceptible to malaria due to hormonal and immunological changes [24]. We also found higher rates of diabetes mellitus among non-pregnant vs. pregnant women with SARS-CoV-2 infection, but lack of detailed data limits interpretation. Furthermore, the association between sickle cell anaemia and ICU admission calls for further investigation on the impact of asplenia and hemoglobinopathy on COVID-19. Finally, we found a higher risk of ICU admission and/or supplemental oxygen use and mortality in Southern and West Africa compared to Eastern Africa, which may reflect regional differences in health system capacities (Southern Africa has the strongest health infrastructure and higher capacity for ICU admissions) and/or severity of SARS-CoV-2 infection related to variant virulence, regional prevalence of HIV infection (highest in Southern Africa), or other unmeasured confounding factors.

Regarding pregnancy-specific outcomes, we found a high rate of caesarean delivery among SARS-CoV-2-uninfected pregnant women. This is likely attributable to our study sites, which comprise referral hospitals where caesarean rates are typically higher than in local hospitals and clinics. SARS-CoV-2-uninfected women were tested secondary to suspected COVID-19 symptoms in our study and may represent a group at higher risk for pregnancy complications compared to pregnant women in general, due to other unmeasured factors. Data on whether SARS-CoV-2 infection is a risk factor for stillbirth are inconsistent [4, 25-27]. Among pregnant women with known pregnancy outcomes in our cohort, the rates of stillbirth, miscarriage, pre-term birth, and low birthweight did not differ based on SARS-CoV-2 infection status. However, our

analyses are likely underpowered and are in contrast with INTERCOVID results, which documented that pregnant women with SARS-CoV-2-infection had higher rates of preterm birth and stillbirth [7]

Our study had some limitations. First, the retrospective cohort design limited collection of some variables of interest (e.g., body mass index) and relied on pooling of available pregnancy data at the time of retrieval from heterogeneous sites in SSA. The establishment of a pregnancy COVID-19 registry has proved challenging in SSA. However, the WHO has set up a global COVID-19 pregnancy prospective cohort study from multiple countries (including in Africa) that will minimize recorder bias [28]. Second, given that comparison groups were not evenly distributed geographically, some identified differences might be explained by regional variations (e.g., HIV prevalence and health infrastructure). Third, we studied only symptomatic women whose symptoms prompted SARS-CoV-2 RT-PCR testing and hospitalization, which included heterogenous control groups with a range of illnesses that could also be associated with adverse pregnancy outcomes, potentially leading to a dilution of differences. Finally, our findings are not necessarily generalizable to asymptomatic pregnant women with SARS-CoV-2 infection who were not hospitalized.

Our findings have important clinical and public health implications. First, given the increased morbidity and mortality in both pregnant vs. non-pregnant women with SARS-CoV-2 infection and in pregnant women with vs. without SARS-CoV-2 infection [4, 29-31], pregnant women (among other at-risk groups) should be prioritized for COVID-19 vaccination in African countries, where vaccine supply is limited but steadily increasing [32, 33]. Although pregnancy was an exclusion criterion in early COVID-19 vaccine and SARS-CoV-2 treatment trials, more trials are enrolling pregnant women [34], preliminary reports do not demonstrate safety issues for pregnant women

receiving mRNA vaccines [35, 36], and several systematic reviews find COVID-19 vaccination in pregnant and lactating individuals is immunogenic, safe with respect to vaccine-related adverse events and obstetrical and neonatal outcomes, and effective [37-40]. Finally, further research is needed to better understand the pathogenesis and optimal management of SARS-CoV-2 infection in pregnancy.

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ACCESS TO DATA STATEMENT: Prof. Jean Nachega and Dr. Rhoderick Machekano had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The dataset used for this study, including individual deidentified participant data and a data dictionary defining each field in the set, will be made available at publication on request to Professor Jean Nachega (jbn16@pitt.edu)

REFERENCES

1. Nachega JB, Sam-Agudu NA, Budhram S, et al. Effect of SARS-CoV-2 Infection in Pregnancy on Maternal and Neonatal Outcomes in Africa: An AFREhealth Call for Evidence through Multicountry Research Collaboration. *Am J Trop Med Hyg*. Dec 28 2020;104(2):461-5. doi:10.4269/ajtmh.20-1553
2. Zambrano LD, Ellington S, Strid P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep*. Nov 6 2020;69(44):1641-1647. doi:10.15585/mmwr.mm6944e3
3. Badr DA, Mattern J, Carlin A, et al. Are clinical outcomes worse for pregnant women at >/=20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. *Am J Obstet Gynecol*. Nov 2020;223(5):764-768. doi:10.1016/j.ajog.2020.07.045

4. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320. doi:10.1136/bmj.m3320
5. Budhram S, Vannevel V, Botha T, et al. Maternal characteristics and pregnancy outcomes of hospitalized pregnant women with SARS-CoV-2 infection in South Africa: An International Network of Obstetric Survey Systems-based cohort study. *Int J Gynaecol Obstet*. Sep 9 2021;doi:10.1002/ijgo.13917
6. de Waard L, Langenegger E, Erasmus K, et al. Maternal and neonatal outcomes of COVID-19 in a high-risk pregnant cohort with and without HIV. *South African Medical Journal* 2021;111(12):1174-1180. doi:DOI:10.7196/SAMJ.2021.v111i12.15683
7. Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. *JAMA Pediatr*. Apr 22 2021;doi: 10.1001/jamapediatrics.2021.1050
8. Sam-Agudu NA, Rabie H, Pipo MT, et al. The Critical Need for Pooled Data on COVID-19 in African Children: An AFREhealth Call for Action through Multi-Country Research Collaboration. *Clin Infect Dis*. Feb 13 2021;doi:10.1093/cid/ciab142
9. Eichbaum Q, Sam-Agudu NA, Kazembe A, et al. Opportunities and Challenges in North-South and South-South Global Health Collaborations During the COVID-19 Pandemic: The AFREhealth-CUGH Experience (as Reported at the CUGH 2021 Satellite Meeting). *Ann Glob Health*. 2021;87(1):90. doi:10.5334/aogh.3440
10. Coker M, Folayan MO, Michelow IC, Oladokun RE, Torbunde N, Sam-Agudu NA. Things must not fall apart: the ripple effects of the COVID-19 pandemic on children in sub-Saharan Africa. *Pediatric Research*. 2020. 2020/09/24. doi:10.1038/s41390-020-01174-y https://doi.org/10.1038/s41390-020-01174-y

11. Massinga Loembé M, Nkengasong JN. COVID-19 vaccine access in Africa: Global distribution, vaccine platforms, and challenges ahead. *Immunity*. Jul 13 2021;54(7):1353-1362. doi:10.1016/j.immuni.2021.06.017

12. Bright B, Babalola CP, Sam-Agudu NA, et al. COVID-19 preparedness: capacity to manufacture vaccines, therapeutics and diagnostics in sub-Saharan Africa. *Global Health*. Mar 3 2021;17(1):24. doi:10.1186/s12992-021-00668-6

13. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. Oct 16 2007;4(10):e297. doi:10.1371/journal.pmed.0040297

14. World Health Organization. Global COVID-19 Clinical Platform with Pregnancy Module–CRF-P. Accessed November 13, 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Pregnancy_CRF-2020.5

15. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94(446):496-509. doi:10.2307/2670170

16. Qeadan F, Mensah NA, Tingey B, Stanford JB. The risk of clinical complications and death among pregnant women with COVID-19 in the Cerner COVID-19 cohort: a retrospective analysis. *BMC Pregnancy Childbirth*. Apr 16 2021;21(1):305. doi:10.1186/s12884-021-03772-y

17. Nachega JB, Ishoso DK, Otokoye JO, et al. Clinical Characteristics and Outcomes of Patients Hospitalized for COVID-19 in Africa: Early Insights from the Democratic Republic of the Congo. *Am J Trop Med Hyg*. 2020;103(6):2419-2428. doi:10.4269/ajtmh.20-1240

18. Abraha HE, Gessesse Z, Gebrecherkos T, et al. Clinical features and risk factors associated with morbidity and mortality among patients with COVID-19 in northern Ethiopia. *Int J Infect Dis*. Apr 2021;105:776-783. doi:10.1016/j.ijid.2021.03.037

19. Martinez-Portilla RJ, Smith ER, He S, et al. Young pregnant women are also at an increased risk of mortality and severe illness due to coronavirus disease 2019: analysis of the Mexican National Surveillance Program. *Am J Obstet Gynecol*. Apr 2021;224(4):404-407. doi:10.1016/j.ajog.2020.12.1197

20. Sigel K, Swartz T, Golden E, et al. Coronavirus 2019 and People Living With Human Immunodeficiency Virus: Outcomes for Hospitalized Patients in New York City. *Clin Infect Dis*. Dec 31 2020;71(11):2933-2938. doi:10.1093/cid/ciaa880

21. Boulle A, Davies MA, Hussey H, et al. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis*. Aug 29 2020; August 29, 2020: doi: 10.1093/cid/ciaa1198. Online ahead of print. doi:10.1093/cid/ciaa1198

22. WHO Global Clinical Platform for COVID-19. Clinical features and prognostic factors of COVID-19 in people living with HIV hospitalized with suspected or confirmed SARS-CoV-2 infection. Accessed October 30, 2021. https://apps.who.int/iris/rest/bitstreams/1356320/retrieve

23. Tadolini M, Codecasa LR, García-García JM, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J*. Jul 2020;56(1)doi:10.1183/13993003.01398-2020

24. McLean AR, Ataide R, Simpson JA, Beeson JG, Fowkes FJ. Malaria and immunity during pregnancy and postpartum: a tale of two species. Parasitology. Jul 2015;142(8):999-1015. doi:10.1017/s0031182015000074

25. Basu JK, Chauke L, Magoro T. Maternal mortality from COVID 19 among South African pregnant women. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2021:1-3. doi:10.1080/14767058.2021.1902501

26. Hcini N, Maamri F, Picone O, et al. Maternal, fetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peripartum period: A single-center prospective comparative study. *Eur J Obstet Gynecol Reprod Biol*. Feb 2021;257:11-18. doi:10.1016/j.ejogrb.2020.11.068

27. Vousden N, Bunch K, Morris E, et al. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS). PLoS One. 2021 May 5;16(5):e0251123

28. World Health Organization. (2020). Global COVID-19 clinical platform with pregnancy module – CRF-P, version 8 April 2020, revised 13 July 2020. World Health Organization. https://apps.who.int/iris/handle/10665/333228. Accessed on March 24, 2022.

29. Katz D, Bateman BT, Kjaer K, et al. The Society for Obstetric Anesthesia and Perinatology Coronavirus Disease 2019 Registry: An Analysis of Outcomes Among Pregnant Women Delivering During the Initial Severe Acute Respiratory Syndrome Coronavirus-2 Outbreak in the United States. *Anesth Analg*. Aug 1 2021;133(2):462-473. doi:10.1213/ane.0000000000005592

30. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *Cmaj*. Apr 19 2021;193(16):E540-e548. doi:10.1503/cmaj.202604

31. Di Mascio D, Sen C, Saccone G, et al. Risk factors associated with adverse fetal outcomes in pregnancies affected by Coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19. *J Perinat Med*. Dec 2 2020;49(1):111-115. doi:10.1515/jpm-2020-0539

32. World Health Organization (WHO) (2021). Joint COVAX Statement on Supply Forecast for 2021 and early 2022. Available at:

https://www.gavi.org/news/media-room/joint-covax-statement-supply-forecast-2021-and early2022?gclid=CjwKCAjwrfCRBhAXEiwAnkmKmaWaizUK1pi7gSSNWBKVwCiGpp2p DUSGyVvQmeOposBlIof8zhR2nxoCbG8QAvD_BwE ; accessed on March 25, 2022 ; accessed on March 25, 2022

33. Guaracio F and Rigby J. COVID-19 vaccine supply for global programme outstrips demand for first time. Healthcare and Pharmaceuticals. February 23, 2022; available at: https://www.reuters.com/business/healthcare-pharmaceuticals/covax-vaccine-supply-outstrips-demand-first-time-2022-02-23/ ; accessed on March 25, 2022.
34. Bianchi DW, Kaeser L, Cernich AN. Involving Pregnant Individuals in Clinical Research on COVID-19 Vaccines. *JAMA*. Feb 10 2021;doi:10.1001/jama.2021.1865
35. Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA COVID-19 vaccines preconception and during pregnancy and risk of self-reported spontaneous abortions, CDC v-safe COVID-19 Vaccine Pregnancy Registry 2020-21. *Res Sq*. Aug 9 2021;doi:10.21203/rs.3.rs-798175/v1
36. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med*. Jun 17 2021;384(24):2273-2282. doi:10.1056/NEJMoa2104983
37. Ciapponi A, Bardach A, Mazzoni A, Alconada T, et al. Safety of components and platforms of COVID-19 vaccines considered for use in pregnancy: A rapid review. Vaccine. 2021 Sep 24;39(40):5891-5908.
38. Girardi G, Bremer AA. Scientific Evidence Supporting Coronavirus Disease 2019 (COVID-19) Vaccine Efficacy and Safety in People Planning to Conceive or Who Are Pregnant or Lactating. Obstet Gynecol, 2022 Jan 1;139(1):3-8
39. Fell DB, Dhinsa T, Alton GD, et al. Association of COVID-19 vaccination in pregnancy with adverse peripartum outcomes. JAMA. 2022 Mar 24. doi: 10.1001/jama.2022.4255. Online ahead of print.

40. Shrotri, Swinnen, Kampmann, Parker (2021). An interactive website tracking COVID-19 vaccine development. Lancet Glob Health; 9(5):e590-e592. Available at : https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/ ; Accessed on March 22, 2022

Table 1. Demographic and Clinical Characteristics by Pregnancy and SARS-CoV-2 Infection Status

	Study Groups					
	SARS-CoV-2-infected Pregnant Women N=510*		**SARS-CoV-2-infected Non-Pregnant Women N=403**		**SARS-CoV-2-uninfected Pregnant Women N=402**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Region						
East Africa	141	28	130	32	98	2
West Africa	56	11	11	3	18	4
Central Africa	79	16	150	37	101	25
Southern Africa	234	46	112	28	185	46
Age group, years						
11-17	4	1	2	1	5	1
18-24	83	16	46	12	85	21
25-34	278	55	181	45	215	54
35-44	110	27	144	36	95	24
45-49	1	0	20	5	0	0
≥50	0		8	2	0	0
Missing/unknown	2		2		2	
Median age (IQR), years	30 (26 – 35)		33 (28 – 38)		30 (25 – 34)	
WHO COVID-19 Stage at admission						
Mild	168	33	230	57	N/A	N/A
Moderate	89	18	24	6	N/A	N/A
Severe	201	39	127	32	N/A	N/A
Critical	52	10	22	6	N/A	N/A
Gestational age at admission						
0 - 12 weeks	29	6	N/A	N/A	18	5
13 - 27 weeks	100	21	N/A	N/A	68	17
28 - 42 + weeks	336	72	N/A	N/A	308	79
Missing/unknown	5		0		10	
Median (IQR) length of hospital stay, days**	8 (5-12)		9 (5–15)		2 (1–7)	

IQR = interquartile range; N/A = not applicable

Includes 12 women from the Democratic Republic of the Congo cohort in Nachega et al. study[17] and 100 women from the South Africa cohort in de Waard et al. study.[19]Median length of hospital stay between pregnant and non-pregnant women with SARS-CoV-2 infection was not significant; however, there was a statistically significant difference between hospital stay for SARS-CoV-2-infected vs -uninfected pregnant women, (p<0.001).*

Table 2. Factors Associated with Intensive Care Unit (ICU) Admission among Pregnant and Non-Pregnant Women with SARS-CoV-2 Infection

Variable	N	Admitted to ICU n (%)	Unadjusted RR (95% CI)	P-value	Adjusted RR* (95% CI)	*P*-Value
Pregnancy Status						
Non-pregnant	403	27 (7)	1		1	
Pregnant	510	95 (19)	2.78 (1.85 – 4.18)	<0.001	2.73 (1.74 – 4.28)	<0.001
Region						
East Africa	271	31 (11)	1		1	
West Africa	67	15 (22)	1.96 (1.12 – 3.41)	0.018	1.13 (0.56 – 2.26)	0.73
Central Africa	176	17 (10)	0.99 (0.61 – 1.62)	0.98	1.17 (0.68 – 2.01)	0.56
Southern Africa	346	50 (14)	1.26 (0.83 – 1.92)	0.27	0.76 (0.44 – 1.30)	0.32
Age group, years						
11 – 17	11	1 (9)	1			
18 – 24	204	20 (10)	.55 (0.08 – 3.62)	0.54		
25 – 34	622	59 (10)	0.74 (0.12 – 4.49)	0.74		
35 – 44	349	36 (10)	0.73 (0.12 – 4.52)	0.74		
45 – 49	21	2 (10)	0.57 (0.06 – 5.27)	0.62		
50+	8	3 (8)	2.25 (0.30 – 16.63)	0.43		
WHO disease stage						
Mild/Moderate	511	16 (3)	1			
Severe/Critical	402	106 (26)	8.42 (5.06 – 14.01)	<0.001		
HIV-positive status						
No	776	90 (12)	1		1	
Yes	137	32 (23)	2.01 (1.40 – 2.89)	<0.001	1.94 (1.18 – 3.18)	0.009
Viral load						
Undetectable	47	12 (26)	1			
Detectable	13	4 (31)	1.21 (0.47 – 3.12)	0.70		
CD4 count (cells/mm^3)						
≥200	75	16 (21)	1			
<200	25	7 (28)	1.31 (0.– 2.82)	0.49		
History of TB						
No	886	112 (13)	1		1	
Yes	27	10 (37)	2.93 (1.74 – 4.93)	<0.001	2.32 (1.17 – 4.58)	0.015
Hypertension						
No	783	96 (12)	1		1	
Yes	130	26 (20)	1.63 (1.10 – 2.41)	0.014	1.37 (0.82 – 2.31)	0.23
Diabetes mellitus						
No	850	107 (13)	1		1	
Yes	63	15 (24)	1.89 (1.18 – 3.04)	0.009	2.01 (1.04 – 3.86)	0.036
Chronic neurological disorder						

No	911	121 (13)	1		1	
Yes	2	1 (50)	3.76 (0.93 – 15.20)	0.06	1.02 (0.12 – 8.49)	0.99
Chronic cardiac disease						
No	897	117 (13)	1		1	
Yes	16	5 (31)	2.40 (1.14 – 5.05)	0.043	1.76 (0.66 – 4.70)	0.26
Chronic pulmonary disease						
No	909	119 (13)	1		1	
Yes	4	3 (75)	5.73 (3.17 – 10.34)	<0.001	1.90 (0.53 – 6.82)	0.32
Acute malaria						
No	898	119 (13)	1			
Yes	15	3 (20)	1.51 (0.54 – 4.21)	0.43		
Asplenia due to sickle cell disease						
No	909	119 (13)	1		1	
Yes	4	3 (75)	5.73 (3.18 – 10.34)	<0.001	6.23 (1.67 – 23.29)	0.007
Cancer						
No	910	121 (13)	1			
Yes	3	1 (33)	2.51 (0.50 – 12.53)	0.26		

*Log-binominal regression *model adjusted for pregnancy status, age, region, non-communicable disease (chronic cardiac disease, hypertension, diabetes mellitus, chronic pulmonary diseases, chronic neurologic diseases, asplenia) and communicable disease (HIV status and history of tuberculosis) comorbidities. WHO COVID-19 staging is not included in multivariable analyses, because its components are in the causal pathway of the primary ordinal outcome.*

Figures 1, 2, 3 and Legends

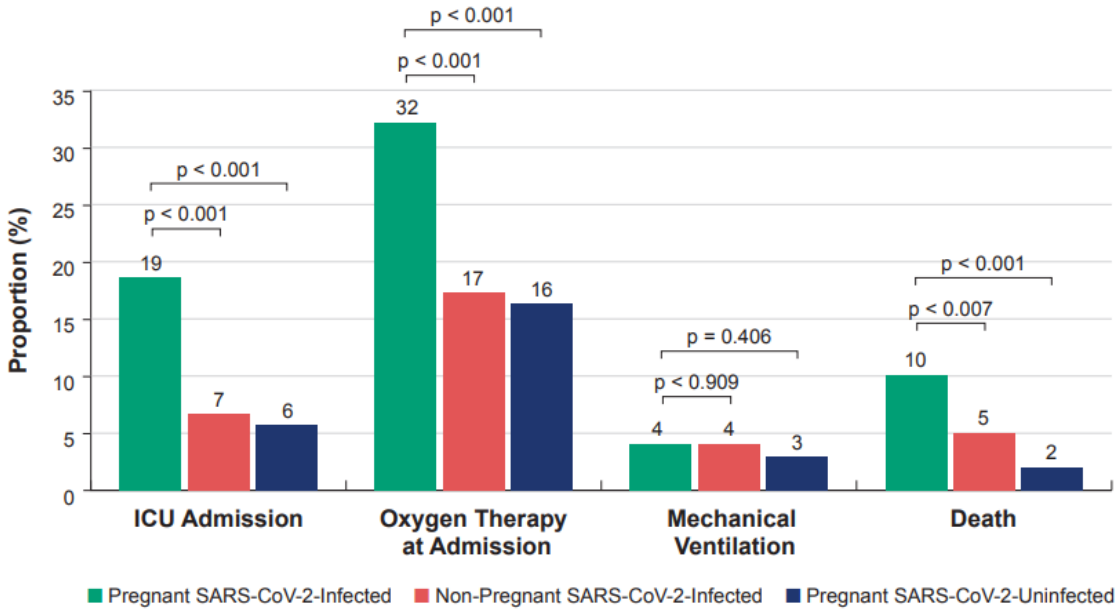
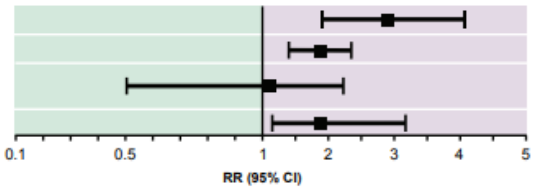


Figure 1. Clinical Outcomes among Pregnant SARS-CoV-2-infected vs. Non-pregnant SARS-CoV-2-infected vs. Pregnant SARS-CoV-2-uninfected Women (Total N = 1,315)

A

Outcomes	Pregnant Women SARS-CoV-2-Infected n (%)	Non-Pregnant Women SARS-CoV-2-Infected n (%)	RR (95% CI)	*P*-Value
ICU Admission	95 (19)	27 (7)	2.78 (1.85 – 4.18)	0.001
Oxygen Therapy	164 (32)	61 (17)	1.86 (1.44 – 2.42)	0.001
Mechanical Ventilation	20 (4)	10 (4)	1.04 (0.50 – 2.20)	0.91
Death	51 (10)	21 (5)	1.94 (1.19 – 3.17)	0.001



B

Outcomes	Pregnant Women SARS-CoV-2-Infected n (%)	Non-Pregnant Women SARS-CoV-2-Infected n (%)	aRR (95% CI)	*P*-Value
ICU Admission	95 (19)	27 (7)	2.38 (1.42 – 4.01)	0.001
Oxygen Therapy	164 (32)	61 (17)	1.81 (1.30 – 2.50)	<0.001
Mechanical Ventilation	20 (4)	10 (4)	0.57 (0.22 – 1.50)	0.26
Death	51 (10)	21 (5)	1.66 (0.95 – 2.88)	0.07

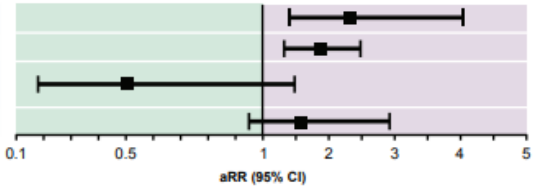
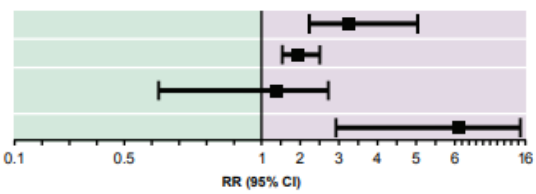


Figure 2. Unadjusted (Panel A) and Adjusted (Panel B) Comparisons of Outcomes between Pregnant (N=510) and Non-pregnant (N=403) Women with SARS-CoV-2 Infection

C

Outcomes	Pregnant Women SARS-CoV-2-Infected n (%)	Pregnant Women SARS-CoV-2-Uninfected n (%)	RR (95% CI)	*P*-Value
ICU Admission	95 (19)	23 (6)	3.26 (2.10 – 5.04)	0.001
Oxygen Therapy	164 (32)	66 (16)	1.96 (1.52 – 2.53)	0.001
Mechanical Ventilation	20 (4)	12 (3)	1.35 (0.67 – 2.72)	0.41
Death	51 (10)	6 (2)	6.70 (2.90 – 15.44)	0.001



D

Outcomes	Pregnant Women SARS-CoV-2-Infected n (%)	Pregnant Women SARS-CoV-2-Uninfected n (%)	aRR (95% CI)	*P*-Value
ICU Admission	95 (19)	23 (6)	2.00 (1.20 – 3.35)	0.008
Oxygen Therapy	164 (32)	66 (16)	1.57 (1.17 – 2.11)	0.002
Mechanical Ventilation	20 (4)	12 (3)	0.90 (0.38 – 2.15)	0.81
Death	51 (10)	6 (2)	3.08 (1.21 – 7.85)	0.001

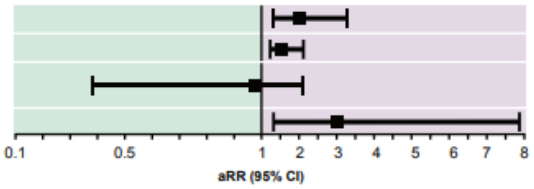


Figure 2. Unadjusted (Panel C) and Adjusted (Panel D) Comparisons of Outcomes between SARS-CoV-2-infected Pregnant Women (N=510) and SARS-CoV-2-Uninfected Pregnant Women (N=402)

Note: The analysis supporting Panels B and D used inverse probability of participation-based weighting (IPPW) to adjust confounding.

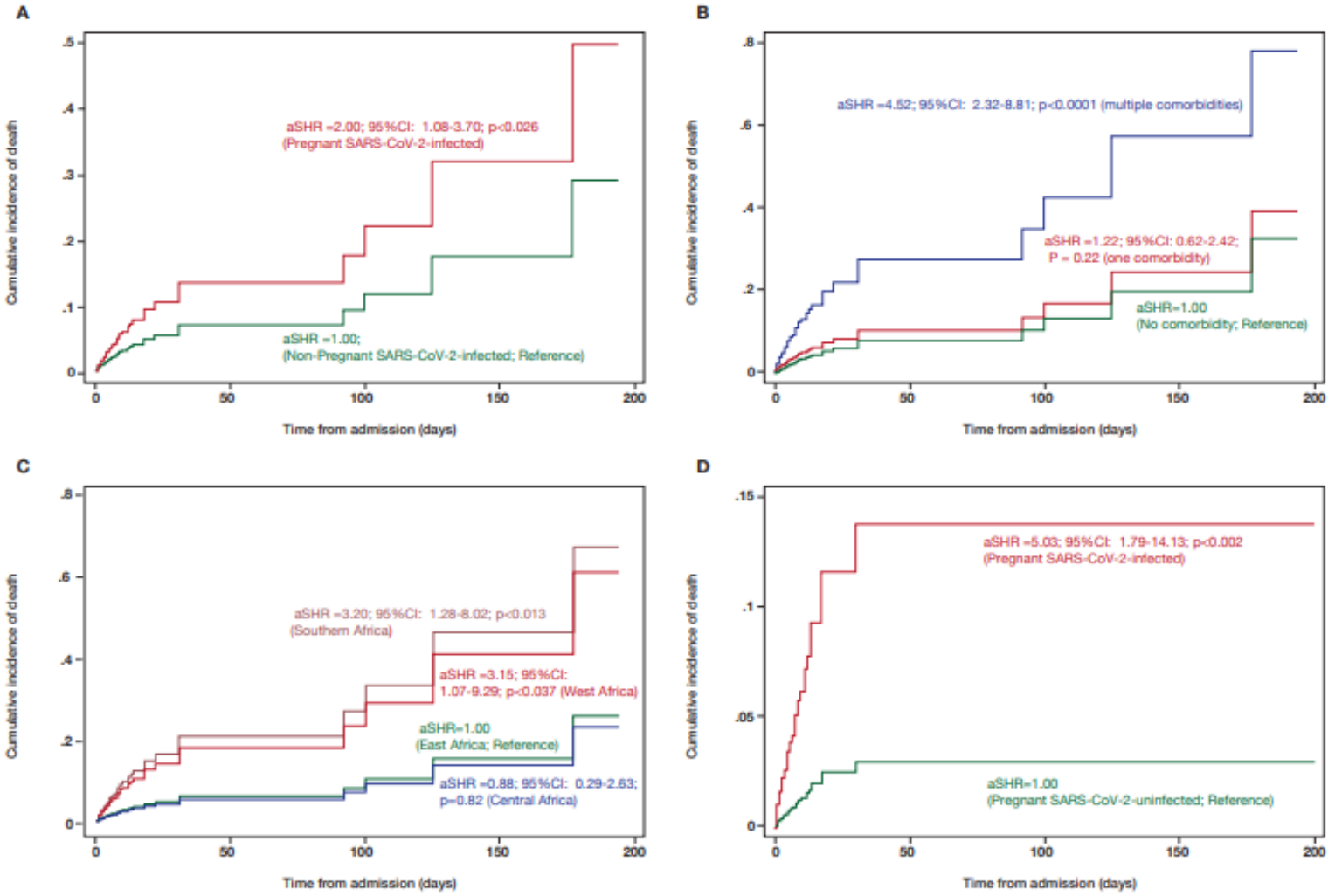


Figure 3: Cumulative Incidence Functions for in-Hospital Mortality in SARS-CoV-2 Infected Women according to Pregnancy Status (Panel A), Number of Comorbidities (Panel B), Region (Panel C), and by SARS-CoV-2 Infection Status in Pregnant Women (Panel D). aSHR: adjusted sub-distribution Hazard Ratio