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TWICE UNLUCKY: FROM EARLY-LIFE CHOLERA EXPOSURE TO ADULT COVID-19 MORTALITY

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Abstract

Many individuals in developing countries experience multiple shocks over their lifetimes, yet the interplay between these shocks is not well understood. This study estimates the impact of prenatal exposure to the cholera epidemic in Peru in the early 1990s on COVID-19 mortality several decades later. We find that a one-standard deviation increase in cholera exposure during the first trimester in utero—measured by regional infection rates—results in a 5% increase in COVID-19 mortality among working-age women. Significant long-term effects on cardiovascular health and economic vulnerability were identified as potential mediators. Given that cholera is the second most common type of epidemic worldwide, this study suggests that policies aimed at reducing the spread of such epidemics could yield substantial long-term benefits. Additionally, countries with a history of cholera may experience disproportionate benefits from COVID-19 vaccination efforts.

Keywords: COVID-19; *cholera; health; human capital; fetal programming*

JEL Codes: I12, I15, I18, I25, O10

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1 Introduction

Recently, the COVID-19 pandemic has led to significant human losses. For many, this has been a once-in-a-lifetime shock, but individuals in developing countries often face multiple shocks over their lifetimes. Little is known about how these shocks interact (Currie and Vogl, 2013). This study aims to address this gap by examining whether prenatal exposure to the cholera epidemic in Peru in the early 1990s affects COVID-19 mortality three decades later.

To investigate this question, we leverage the quasi-random variation in cholera infection rates across Peru, which resulted from several factors. Firstly, the cholera epidemic was unexpected, marking the return of the disease to Latin America after a one-hundred-year absence (Lam et al., 2010). As noted in a New York Times article "Disease control experts are largely at a loss to explain why cholera has returned to South America in the first epidemic since 1895"(Brookes, 1991).

Secondly, initial cases were influenced by the ecological conditions of the Pacific Ocean (Gotuzzo, 1991). The spread from these initial cities to other parts of the country occurred rapidly and was primarily determined by their geographic proximity to the first outbreaks. Finally, the intensity and duration of the epidemic in each region were largely shaped by factors such as temperature, rainfall, and altitude.

Unsanitary conditions also contributed to the rapid spread of the disease. However, we find no significant correlation between unsanitary conditions and the variation in cholera intensity that we exploit. This is expected, as we account for regional fixed effects and region-specific trends. Additionally, poor sanitation has been a widespread and persistent issue throughout Peru, with inadequate chlorination of piped water during that period

(Cueto, 2017). As a result, no household was spared from potential exposure to the epidemic.

We estimate an event study and a two-way fixed effect model, comparing the outcomes of individuals within regions but that were in-utero in different times relative to the beginning of the epidemic. We apply a Two-Stage Approach following Borusyak et al. (2022) and Gardner (2021). This methodology is well-suited to our context because it addresses potential issues associated with two-way fixed effects models when treatment is staggered and varies over time (Goodman-Bacon, 2021*a*), while allowing for a non-binary treatment.

Our analysis reveals that working-age women exposed to cholera during the first trimester in utero are more likely to die from COVID-19 three decades later. Specifically, a one standard deviation increase in cholera prevalence increases COVID-19 mortality by 5%.

To explore potential mechanisms, we investigate two types of channels. First, we examine biological channels. Cardiovascular diseases and obesity are significant medical risk factors for COVID-19 mortality (Chiappetta et al., 2020; Wu and McGoogan, 2020; Zhou et al., 2020). We construct an index of "cardiovascular vulnerability" based on measurements of obesity rates and high blood pressure. Our findings show that a one-standard deviation increase in cholera prevalence during the first trimester in utero increases long-term cardiovascular vulnerability by 0.04 standard deviations.

Second, we explore potential behavioral channels, as risky behaviors and poor living conditions can increase the likelihood of COVID-19 infection and mortality. For instance, less educated individuals may be less compliant with mask mandates, social distancing, and lockdowns due to limited access to information compared to those with higher education (Case and Deaton, 2021). Similarly, informal and self-employed workers are less likely to adhere to lockdowns and social distancing measures, as missing work means losing in-

come. Additionally, household crowding can elevate the risk of contagion among family members. High levels of self-employment, informality, and household crowding have been major factors contributing to the Peruvian government's struggle to contain the epidemic despite their swift response and nationwide lockdown (Bel, 2020). We construct "economic vulnerability" index based on educational attainment, self-employment, and household crowding and find that a one standard deviation increase in the cholera prevalence during the first trimester in-utero increases long-term economic vulnerability by 0.07 standard deviations.

We find a positive but statistically insignificant effect on reported COVID-19 cases. The reported cases of COVID-19 during the first year of the epidemic in Peru are a poor proxy for the actual prevalence of the disease, and our analysis lacked the power to detect small effects. Therefore, we cannot rule out the possibility that economic vulnerability might be a key channel through which prenatal cholera exposure increases COVID-19 mortality.

Additionally, we find the following reassuring results: First, event studies reveal no evidence of pre-existing trends. Second, placebo regressions show no effect of exposure to the cholera epidemic prior to conception. Finally, we find that women who were in their first trimester during the cholera epidemic were not more obese, less educated, or economically vulnerable compared to other women.

With this study we aim to contribute in several ways. First, we add to the literature on the long-term effects of early-life shocks. Extensive research has documented the enduring consequences of prenatal shocks on health and human capital (Almond and Currie, 2011), and more recent studies have explored their impact on adult mortality (Goodman-Bacon, 2021*b*; Duque and Schmitz, 2023; Hollingsworth et al., 2024; Fletcher and Noghanibehambari, 2024; Noghanibehambari, 2022; Noghanibehambari and Fletcher, 2024).

However, few studies examine how early-life exposure to one negative shock influences the effects of subsequent shocks later in life, despite many individuals experiencing multiple negative shocks. Theoretically, it is unclear whether an early-life shock will exacerbate or mitigate the effects of another later shock. Models of dynamic complementarities between shocks predict an intensification effect (Cunha and Heckman, 2007), while models of social learning (Agüero and Beleche, 2017) and biological adaptation (Fink, Venkataramani and Zanolini, 2021) predict an attenuation effect.

Second, this study aims to contribute to the understanding of early-life contributors of COVID-19 mortality. COVID-19, and similar epidemics, will be most likely part of the future (WB, 2017). This study provides evidence that early-life circumstances can have a powerful impact on COVID-19 mortality. Moreover, this study suggests that countries with a history of cholera exposure, and in particular, individuals exposed to cholera in-utero may benefit disproportionately from COVID-19 vaccination.

Finally, this study aims to contribute to public knowledge about the long-term consequences of cholera epidemics. While cholera has received considerably less attention than the COVID-19 pandemic, it has been the second most common type of epidemic worldwide over the past two decades (Smith et al., 2014). This year alone, 29 countries have reported cholera cases, including several large outbreaks (World Health Organization). The long-term consequences on cardiovascular health, economic vulnerability, and COVID-19 mortality should alert policy makers about additional and substantial costs of cholera epidemics. The mortality of working-age individuals is particularly critical in less developed countries, where limited life insurance, labor benefits, and institutional support for widows can push families into a poverty trap following the death of a working-age member.

2 Peru: COVID-19 in 2020 and cholera in 1991

Peru was one of the first countries to impose a mandatory lockdown in March 2020. During that time COVID-19 had caused only a few deaths in the country, while in other countries it was expanding explosively. Moreover, the lockdown was extended five times and complemented with curfews throughout much of 2020 and part of 2021. Despite these precautionary government measures, Peru has experienced the highest Covid mortality rates per capita and one of the highest Covid case-fatality ratio in the world.

While the reasons for Peru's high mortality rates remain unclear, experts have identified several probable causes (Bel, 2020). First, the significant proportion of informal workers and self-employed individuals, who are less likely to adhere to lockdowns and other social distancing measures, is a major factor. It is estimated that approximately 70% of workers in Peru are employed informally, and 40% are self-employed (Jaramillo and Ñopo, 2020). Other potential contributors include high population density in markets, banks, and households, coupled with inadequate and insufficient healthcare infrastructure, which led to the saturation of the health system. These factors appear to be major contributors to the severe impact of the COVID-19 epidemic in Peru.

In this paper, we explore an additional potential contributor: the history of cholera. In early 1991, a cholera epidemic struck Peru. The disease spread rapidly throughout the country, and by the end of 1991, it had reached fourteen countries in Latin America and the Caribbean, totaling 366,017 cases, with Peru accounting for 83% of all cases in the Americas (Mujica, Gomez Mujica and Gomez, 1991). Figures 1 and 2 illustrate how Peru has had the highest COVID-19 mortality and the highest accumulated cholera incidence in the latter half of the 20th century.

The cholera epidemic was abrupt, unexpected, and spread very rapidly. The first cases

appeared at the end of January 1991. It is important to clarify that these were believed to be the first cases in Peru, not just the first to be reported because groups of adults and children were routinely tested before 1991 for several diseases including the bacterium *Vibrium cholerae,* which was not identified (Gotuzzo, 1991). Despite these routine tests, a cholera outbreak was not expected at that time, because there had been no evidence of cholera in the whole of Latin America for the previous 100 years.

The disease was first reported in the areas around the coastal cities of Chancay, Chimbote, and Piura. Cholera is more likely to develop in coastal ecologies (Collins, 2003); apparently, the warm part of the sea in Peru is an ideal environment for the bacterium to develop and contaminate phytoplankton and other sea life (Gotuzzo, 1991). From there, the epidemic advanced to the adjacent regions and over time reached the rest of the country, as can be seen in Figure 3.

Other important factors that seem to affect the spread and intensity of the epidemic were temperature, rainfall, and altitude (Lama et al., 2004). Figure 4 shows the changes in cholera incidence by geographical region. We can observe that cases peaked first in the coastal region but declined shortly afterward, with the beginning of the winter season and cases raised again in the summer months of 1992. The cases in the highlands started sometime after the cases in the Coast, but they never reached similar prevalence rates, presumably because of the altitude and colder temperatures in that region. Finally, the cases appeared the last in the Jungle region and generated the highest prevalence rates. We can also see that the cases here stayed relatively high during almost the entire year of 1991, coinciding with the high temperatures that prevail in the Jungle region all year around, but decreasing at the end of the year with the rainy season.

Finally, inadequate levels of basic sanitation, particularly the insufficient treatment of

drinking water, is believed to have contributed to the spread of the epidemic (Gotuzzo, 1991). However, as detailed in the Robustness Section, we find no significant correlation between sanitation variables (such as piped water at home and open defecation) and the variation in cholera intensity (measured by cases, not deaths) that we examine. This finding is not surprising, given that poor sanitation has long been a persistent issue in Peru, with such conditions prevailing throughout the country at that time; even piped water was inadequately chlorinated (Cueto, 2017). Consequently, no household was immune to potential exposure to the epidemic.

3 From Cholera to COVID-19 Mortality: Potential Channels

Cholera is considered an acute diarrheal disease caused by the bacterium Vibrium Cholerae. The main cause of death associated with this infection is severe dehydration. Likewise, among pregnant women, it affects the fetus mainly through maternal dehydration; pathogens damage the intestines, causing an excessive amount of water and other nutrient-rich fluids to be secreted rather than being absorbed (Grados and Battilana, 1994; Grout et al., 2015; Hirschhorn, Chowdhury and Lindenbaum, 1969; Ciglenecki et al., 2013).

Prenatal exposure to a cholera epidemic can have long-term effects, for several reasons. First, as Barker (1990) and later Gluckman and Hanson (2006) have argued, individuals who suffer from intrauterine starvation are more likely to be obese, and suffer from cardiovascular disease and type-II diabetes. Epidemiological as well as economic studies have found empirical evidence that exposure to nutritional deprivation, especially *during the first trimester*, has a significant impact on these health outcomes (Ravelli, Stein and

Susser, 1976; Stein et al., 2007; Painter, Roseboom and Bleker, 2005; Fung, 2009; Hoynes, Schanzenbach and Almond, 2016). Cholera, like other acute diarrheal diseases, resembles acute starvation in its effects since it reduces dietary intake and intestinal absorption of nutrients (Brown, 2003). During the Peruvian cholera epidemic, it was reported that in severe cases, patients lost a significant percentage of body weight in just a few hours (Cueto, 2017). Moreover, Ritter and Sanchez (2022) find that prenatal exposure to the cholera epidemic increased childhood mortality and surviving children exposed to cholera *during their first trimester* are more likely to have lower weight-for-age and have a greater likelihood to be underweight.

Second, lower in-utero nutritional intake can have long-term effects on other health outcomes, as well as on human capital and labor outcome variables. Although the biological mechanisms underlying these effects are less well understood, there is substantial empirical evidence supporting their presence (Almond and Mazumder, 2011; Majid, 2015; Hoynes, Schanzenbach and Almond, 2016). Specifically related to exposure to cholera and waterborne diseases, Ogasawara and Inoue (2018) find that prenatal exposure to cholera reduces adult height, while Venkataramani, Bhalotra et al. (2013) find that early-life exposure to Mexico's National Clean Water Program results in increased adult height for men and school completion for women. Beach et al. (2016), using early-life reduction in typhoid fatality rates to proxy for water quality, find impacts on later-life earnings and educational attainment. Chen, Li and Xiao (2022) show that early-life exposure to tap water increases cognitive test scores at ages 10–15.

Finally, as with most epidemics, the cholera epidemic in Peru represented an income and stress shock for many families (Cueto, 2017), and there is evidence of the detrimental long-term effects of those types of shocks too (Almond and Currie, 2011; Almond, Currie

and Duque, 2018). Moreover, an epidemic can overwhelm the healthcare system, reducing its ability to attend to patients, including pregnant women. In the particular case of prenatal exposure to the cholera epidemic in Peru, Ritter and Sanchez (2022) find that it decreased antenatal care and institutional deliveries.

It is possible, therefore, that prenatal exposure to the shocks brought by a cholera epidemic increases the likelihood of COVID-19 mortality. The effect could be direct or indirect as shown in Figure 5. We can think of at least two potential channels. First, we know that controlling for age, cardiovascular diseases are the most important medical risk factors for Covid mortality (Chiappetta et al., 2020; Wu and McGoogan, 2020; Zhou et al., 2020). Given the evidence that nutritional deprivation has long-term effects on obesity and related diseases, this represents a possible channel through which prenatal exposure to cholera could affect Covid mortality.

Second, individuals who do not comply with health and social distance recommendations are more likely to contract and, consequently, die from Covid. Three specific groups are particularly prone to non-compliance with these recommendations: less-educated individuals, the self-employed and those working in the informal sector, and those living in overcrowded households. Less-educated individuals are less likely to follow these recommendations, presumably due to limited access to information (Case and Deaton, 2021). Informal and self-employed individuals are less likely to comply because missing a day of work means losing income. Finally, individuals living in overcrowded households face a higher risk of infection due to limited opportunities for social distancing. Given the evidence that a range of prenatal shocks can have long-term effects on human capital and economic outcomes, prenatal exposure to the cholera epidemic might influence COVID-19 infection and mortality through these behavioral risk factors.

4 Data and Summary Statistics

The data used in this paper comes from four sources of secondary information. The first source is the number of cases of cholera registered in Peru disaggregated by week-year and region (with the exception of Apurimac and Madre de Dios) from years 1991 to 1995. For our main analysis, however, we focus only on the early stages of the epidemic in each region (up to February 1992 for the regions affected last), as explained in more detail in the next section. This data was obtained from a report elaborated by the General Directorate of Epidemiology, of the Ministry of Health of Peru (Suárez-Ognio, 2011). Cholera cases were not identified before 1991, despite routine testing (Gotuzzo, 1991), so we assigned zero cases for the years prior.

The second data source used in this study is the Demographic and Family Health Survey - DHS conducted by the National Institute of Statistics and Informatics - INEI from Peru, which collects health and economic information of adult women. We use survey years with at least one treated cohort, that is DHS from 2009 to 2019. Our analysis is limited to women because this dataset does not include information on adult men. Since the regressors vary only by region and date of birth, we aggregate this data set also by region and date of birth after controlling for age and race. The Appendix provides estimates without controlling for these variables.

The third source of data is the 1992 DHS, which provides information about adult women and their children ages 0 to 5. We use this data set to compare women whose children were in the first trimester in-utero during the cholera epidemic with women whose children were in-utero before the epidemic.[1]

[1] This is the only round suitable for this comparison because the nearest alternative rounds, the 1986 DHS and the 1996 DHS, do not include women with children exposed to the epidemic in utero.

Finally, the fourth data source is the official count of COVID-19 cases and deaths for 2020, the first year of the COVID-19 epidemic, by region and birthdate provided by SINADEF (Sistema Informatico Nacional de Defunciones). To obtain the rates of cases and deaths relative to the population, we use the regional population data by birthdate from the 2017 Census.

We merge all data sets at the region and cohort levels and limit our final sample to women aged 60 or younger (i.e., born in 1960 or later). Table 1 presents the summary statistics of the main variables used in this study for the main period of analysis. The average COVID-19 mortality rate among these working-age women in 2020 was 0.39 per 1,000, while the average COVID-19 infection rate in 2020 was 214 per 1,000. For cohorts born between September 1991[2] and February 1992, the average prevalence of cholera was 5.9 cases per 1,000. 24% of women are classified as obese and 29% having elevated blood pressure. Additionally, the average educational attainment is 10 years, 36% of women are self-employed, and the average household crowding is 2.5 individuals per bedroom. Elevated levels of obesity and household overcrowding are common in Latin American countries. Similarly, high levels of self-employment are prevalent in developing countries, often reflecting a response to the scarcity of formal jobs (Leal Calderon and Chacón, 2017).

5 Empirical Strategy

To investigate the long-term effects of in-utero exposure to the cholera epidemic, we exploit the abrupt onset of the cholera epidemic by estimating an event study and a two-way fixed

[2]Cohorts born before September 1991 did not experience cholera during their first trimester in utero.

effect model with a continuous treatment. Our treatment variable is the rate of cholera cases per region during the first trimester in utero, based on birthdate and assuming a gestation period of 38 weeks. [3]

We focus on the first trimester guided by previous findings from the fetal-programing literature, which indicate that nutritional deprivation during this period has significant long-term consequences, as discussed in Section 3. Additionally, cholera cases fluctuated considerably by trimester, so focusing on the cholera rate during a single trimester allows us to capture more variation in our regressor. As we will see in the Event Studies, exposure during other trimesters does not show significant effects.

Regions are categorized into three treatment groups and one control group based on the starting month of the cholera epidemic in each region.[4] The first group comprises five regions, the second group includes eight regions, the third group consists of seven regions, and the control group is made up of three regions.

We use a two-stage imputation approach following Borusyak and Jaravel (2018) and Gardner (2022). This methodology is particularly suited for our analysis because it addresses the potential issues associated with two-way fixed effects models when treatments are staggered and vary over time (Goodman-Bacon, 2021*a*) while allowing for non-binary treatments. This methodology estimates what the outcomes would have been in the absence of treatment using only not-yet and never treated observations. In the first stage, it estimates the residual of the outcome variables after controlling for fixed effects, trends, and control

[3]The DHS does not provide the exact day of birth, so we assume all children were born on the 15th of the month. Additionally, the DHS lacks information on gestational length, so we follow the medical literature by assuming a gestation period of 38 weeks and the first 10 weeks correspond to the first trimester.

[4] A cohort is classified as treated if there was at least 1 case of cholera out of 1,000 inhabitants in the region during the first trimester in-utero.

variables using only not-yet and never treated observations. In the second stage, it regresses the outcome residuals estimated in the first stage on the treatment variable.

Our non-parametric event study follows a model similar to those used by Alpert, Powell and Pacula (2018) and others. It is structured as follows :

$$Y_{r,m,y} = \alpha_o + \sum_{t=-10}^{0} \beta_t \overline{Chol}_r \times T_{t,s} + \gamma_1 X_{r,m,y} + \phi_r tr + \alpha_r + \rho_{m,y} + \varepsilon_{r,m,y}$$

where $Y_{r,m,y}$ denotes the outcome of women born in month m, and year y, who currently lives in region r. $\overline{Chol}_r$ represents the regional average of the cholera incidence during the first trimester in-utero of the first 3 cohorts of region r that were fully affected by the epidemic. For instance, in regions first affected by the cholera epidemic, we average the cholera incidence experienced during the first trimester in utero for cohorts born in October, November, and December 1991. Conversely, for regions affected last, we average the cholera incidence experienced during the first trimester in utero for cohorts born in December 1991, January 1992, and February 1992.

We limit the effect to the first three cohorts for several reasons. First, our treatment variable (cholera incidence) varies not only across regions but also over time, and as explained in Section 2, it fluctuates significantly by season. By averaging only the first three cohorts, we minimize the risk of the treatment "turning off." Additionally, focusing on the first three cohorts helps reduce the potential for selection bias; the cholera epidemic was unexpected at its onset, but less so later on. Women might have chosen to delay pregnancy in response to the epidemic, and over time, individuals began to learn strategies to mitigate the effects of cholera infection. We explore the potential effects of the epidemic on fertility and selection and include estimations with additional cohorts in the Robustness Section.

$T_{t,s}$ represents a series of indicator variables denoting when individuals were born relative to the beginning of the epidemic in their region. For example, in regions treated first, T_0 equals to one for cohorts born in September, who were partially exposed to the epidemic during their first trimester, depending on the exact day of birth and gestational length. T_1, T_2, and T_3 are equal to one for cohorts born in October, November, and December 1991, respectively. These individuals were fully exposed to the cholera epidemic during their first trimester in-utero, assuming a complete gestational period. In the Robustness Section, we estimate the effects of exposure to the cholera epidemic assuming different gestational periods. Our data is balanced in terms of leads and lags for each group of regions.

$\phi_r t$ represents region-specific trends, α_r represents region-fixed effects, and $\rho_{m,y}$ represents month-year of birth fixed effects. $X_{r,m,t}$ stands for temperature and precipitations by month-year and region and age and ethnicity of the women when we use the DHS data (with the COVID-19 mortality data, we cannot separate age from date of birth, as we only have data for one year and lack information on race). In the Appendix, we provide estimations without including control variables.

Standard errors are clustered at the region-by-month-and-year level. For robustness, we also report p-values from standard errors clustered only at the regional level, using Wild Bootstrap inferences, to correct for the small number of regions, following Cameron, Gelbach and Miller (2008).

The main variables of interest are the full set of β_t estimates, which we will present graphically. $\beta_1$to β_3 give us the effect of the exposure to a 1 standard deviation increase in cholera incidence during the first trimester in-utero for cohorts that were fully exposed. β_{-1} to β_{-10} give us the effect of the epidemic on individuals who live in the same regions but were in their first trimester before the epidemic started.

Note that even in the absence of pre-existing trends, β_t for $t < 0$ are not necessarily equal to 0, as they capture the long-term effects on mortality from exposure to cholera in other trimesters and after birth. However, if the event study does not show a long-term trend in increasing mortality rates leading up to the cholera epidemic, then that is evidence that our effects are not endogenously driven by omitted variables correlated with the spread of the epidemic.

Our second specification is as follows:

$$Y_{r,m,y} = \beta_o + \beta_i Ch_{r,m,y} + \gamma_1 X_{r,m,y} + \phi_r tr + \alpha_r + \rho_{m,y} + \varepsilon_{r,m,y}$$

This model exploits the full variation of the cholera infection rate both across regions and over time; it captures the variation in cholera exposure across cohorts within treated regions. Additionally, this model enhances the precision of our estimates by pooling data from periods before and after exposure to the cholera epidemic during the first trimester in utero.

6 Results

Figure 6 presents the estimated event studies. Cohorts exposed to the cholera epidemic during the first trimester in-utero had a significantly higher probability of dying from COVID-19 thirty years later. Specifically, a one standard deviation increase in the incidence of cholera during the first trimester in-utero increases Covid mortality rate by an average of 0.019 deaths per 1,000 inhabitants or 5% among working-age women. The event study also indicates no significant effects of postnatal exposure and shows no evidence of pre-existing trends.

To explore potential mediators, we begin with biological risk factors associated with cardiovascular diseases. According to the World Health Organization, these risk factors include elevated blood pressure, raised blood glucose, raised blood lipids, and obesity. However, our data only includes measures of blood pressure and obesity. Therefore, we construct our index as a simple average of standardized measurements of obesity rates and elevated blood pressure[5], following methodologies from Kling, Liebman and Katz (2007), Hoynes, Schanzenbach and Almond (2016) and others.

It is important to note that our blood pressure measures come from a not-necessarily random subsample of women, covering about one-third of the sample. Consequently, results should be interpreted with caution, nevertheless, Figure A1 of the Appendix shows the event studies of obesity and elevated blood pressure, separately, and a similar pattern can be observed for both.

The event study of cardiovascular vulnerability presented in Figure 6 is somewhat noisy but indicates higher values for cohorts exposed to the cholera epidemic during their first

[5]Elevated blood pressure is defined as a systolic pressure between 120 and 129 mmHg, with a diastolic pressure of less than 80 mmHg, following the guidelines set by the National Institute on Aging.

trimester in utero, particularly for the second cohort. Specifically, an increase in one standard deviation in the incidence of cholera during the first trimester in-utero increases cardiovascular vulnerability by an average of 0.04 standard deviations among working-age women. The event study also reveals a few significant effects of postnatal exposure and exposure during the second trimester in utero; however, overall, the graph shows no evidence of pre-existing trends.

To explore potential behavioral risk factors, we construct a "economic vulnerability index". This index is a simple average of standardized measurements of self-employment, house crowding and education (in negative) again following the methodologies of Kling, Liebman and Katz (2007), Hoynes, Schanzenbach and Almond (2016) and others. Figure A1 in the Appendix in the Appendix displays the event studies for educational attainment, self-employment, and household crowding individually, showing a very similar pattern across these outcomes.

The event study in Figure 6 reveals that cohorts exposed to the cholera epidemic during the first trimester in utero exhibit a higher probability of economic vulnerability in adulthood. Specifically, an increase in one standard deviation in the incidence of cholera during the first trimester in-utero increases economic vulnerability by 0.08 standard deviations among working-age women. The event study also shows no significant effect of postnatal exposure and no evidence of pre-existing trends.

Finally, we examine the impact on reported COVID-19 cases. The event study in Figure 6 indicates an increase in reported COVID-19 cases for the second and third cohorts exposed to cholera. Specifically, an increase in one standard deviation in the incidence of cholera during the first trimester in-utero increases reported cases by an average of 5 cases per 1,000 inhabitants or 2%. However, this average effect is not statistically significant.

It is important to recognize that the setting used to estimate the impact on infection rates may not be ideal. The statistical power to detect an effect of this magnitude is relatively low (around 20%). Additionally, reported COVID-19 cases may be an inadequate proxy for actual infection rates, as many cases went unreported. Factors contributing to this include a high prevalence of asymptomatic cases, particularly among younger individuals; limited incentives to report cases due to the lack of effective treatments and fear of contagion in healthcare settings[6]; and, specifically in Peru, compromised accuracy of reported cases during the first year of the epidemic due to a saturated healthcare system and a shortage of quality testing.[7]

In summary, our findings suggest that the cholera epidemic increased COVID-19 mortality primarily through a biological channel, as evidenced by worsened cardiovascular health. Additionally, there may be a potential behavioral channel, as increased economic vulnerability could have contributed to higher COVID-19 infection rates. However, our estimation of the effect on COVID-19 infection rates is imprecise, leaving the evidence regarding the behavioral channel inconclusive.

Tables 2 and 3 present the estimations of our parametric model. These findings are consistent with those from the event studies. The tables also include separate estimates for the components used to construct our cardiovascular and economic vulnerability indexes. Although estimating these variables individually reduces statistical power, the results indicate effects in the expected directions.

Table 2 reports the impact on COVID-19 mortality and biological mediators. A 1

[6]It is important to note that this was not the case for the cholera epidemic. Cholera treatment was highly effective, and there was minimal fear of contagion in healthcare facilities, as cholera is not an airborne disease.

[7]As of July 2020, 73% of COVID-19 cases in Peru were diagnosed using rapid tests, while only 27% were diagnosed with polymerase chain reaction (PCR) tests. Peru was one of the few countries that relied predominantly on rapid tests, contrary to the World Health Organization's recommendations (OjoPublico, 2020).

standard deviation in the incidence of cholera during the 1st trimester in-utero increases COVID-19 mortality rate by 0.0018 percentages points, obesity rate by 0.5 percentages points, and elevated blood pressure by 0.4 percentages points (though the latter is not statistically significant).

Table 3 shows the effects on COVID-19 mortality and behavioral mediators. A one standard deviation increase in cholera incidence during the first trimester in utero leads to a reduction in educational attainment by 0.03 years, an increase in self-employment by 0.6 percentage points, an increase in household crowding by 0.03 individuals per bedroom, and an increase in COVID-19 reported cases by 4.4 per 1,000 (though this effect is not statistically significant).

The effects observed are relatively small in magnitude. However, it is important to consider that the affected women are still relatively young, and the fetal origins hypothesis suggests that long-term effects may remain latent for extended periods (Almond and Currie, 2011). Therefore, the impacts, particularly on cardiovascular health, may become more pronounced as individuals age. Additionally, data limitations prevent us from calculating a more comprehensive index of cardiovascular health, which should ideally include measures such as blood glucose and blood lipids. Furthermore, cholera infections were associated with miscarriages (Saona et al., 1991), meaning that those who survived the epidemic might represent a healthier subset of the population (Bozzoli, S. Deaton and Quintana-Domeque, 2007; Currie and Vogl, 2013). As a result, these estimates could be lower bounds of the true effects.

7 Robustness

The cholera epidemic might have influenced migration patterns, with individuals potentially relocating from heavily affected areas to less-affected ones. Such an avoidance behavior could reduce the observed impact of the epidemic. However, if the migration was selective—favoring families of certain characteristics—our estimates might reflect compositional changes rather than the direct effects of early-life cholera exposure.

We only have data on individuals' current regions of residence, not their regions of birth. Therefore, if migration due to cholera was selective, our results would still reflect the causal impact of the cholera epidemic on COVID-19 mortality. However, the mechanism might be attributed to changes in the population composition resulting from the relocation of some families. While we cannot fully rule out this possibility, for migration to significantly affect our estimates, it would have needed to disproportionately displace families with children in the first trimester of gestation compared to those with children in later trimesters or older children. Such a scenario seems unlikely.

The cholera epidemic could have also discouraged some mothers from becoming pregnant. If the epidemic led to a reduction in pregnancies, our estimated effect could be attenuated by this avoidance behavior. Alternatively, if only a selected group of mothers was deterred from getting pregnant, this could explain some of our results. In such a case, we would expect that the cholera incidence during the trimester *before* conception would have a stronger effect on altering the composition of pregnant women than the incidence during the first trimester of pregnancy. Since the incidence of cholera during the trimester before conception can be correlated with the incidence of cholera during the first trimester in-utero, it is possible that our estimates were endogenously driven by this correlation.

To test this alternative explanation, we conduct a placebo regression using cohorts that were exposed to the cholera epidemic before conception. Specifically, we include data on three additional cohorts that were exposed to the initial stages of the epidemic prior to conception. Although these cohorts were exposed to the remainder of the epidemic while in utero, we estimate the placebo effect of exposure to the epidemic before conception while controlling for exposure during the first trimester in utero. Tables 4 and 5 indicate that cholera incidence during the trimester before conception is not associated significantly with any of the main outcomes except with household crowding. In this case, however, the association is negative: cholera incidence during the trimester before conception is associated with *less* household crowding.

Note that Tables 4 and 5 also present the effects of exposure during the first trimester in utero for the first six cohorts that were fully affected by the epidemic, rather than just the initial three cohorts. A comparison between Tables 4 and 5 and Tables 2 and 3, reveals that the estimates are very similar.

Additionally, we use the DHS 1992 data to examine differences in fertility and the composition of women who were in their first trimester during the cholera epidemic. Table 6 indicates no significant effect on the number of children born, suggesting that the cholera epidemic did not impact the fertility rate of average women. [8]

The table also reveals that women who were in their first trimester during the cholera epidemic were not more obese, less educated, or more economically vulnerable compared to others. These findings provide evidence against potential compositional changes in the mother, as well as against potential endogeneity in our empirical model, as they show that

[8] Since this survey was conducted during the epidemic (at the end of 1991 and the beginning of 1992), the number of children reported would accurately reflect any impact on fertility during that period. In contrast, data from later surveys might include children born after the epidemic, potentially offsetting any decrease in fertility that occurred during the epidemic.

the epidemic was not more severe in regions where women were more obese or less educated. This result is consistent with the notion that changes in obesity rates or educational attainment typically occur gradually, and we did not observe any pre-existing trends in our main results.

In a similar vein, columns 5 and 6 test whether regions with poorer sanitation—measured by the percentage of households with piped water and the percentage of households practicing open defecation—experienced higher cholera infection rates.[9] We find no evidence that cohorts with greater exposure to the cholera epidemic were less likely to have piped water at home or more likely to defecate in the open.

Note that Table 6 has significantly fewer observations for estimating these effects compared to our original estimations. This limitation arises because the DHS 1992 data only covers cohorts born only between late 1986 and 1991 and aggregates information across 15 regions, resulting in less variation. For comparison, Tables A1 and A2 in the Appendix replicate Tables 2 and 3, but only for the same cohorts and regions used in the placebo regressions. The effects on our main outcomes continue to be statistically significant, indicating that the smaller number of cohorts and regions should not prevent us from estimating moderate-sized effects.

Finally, up to this point, we have assumed a 38-week gestation period. However, the cholera epidemic may have affected pregnancy length. To assess whether this assumption significantly impacts our results, we test alternative gestation periods of 36 weeks and 34

[9]Ideally, we would have data on these variables from the time each cohort was in utero. However, we only have information from 1991, the year of the epidemic. Thus, we are assuming that these variables did not change significantly between 1987 and 1991. This assumption is less critical than it might appear. Households usually progress from lacking piped water to having it, rather than the other way around, and the same pattern generally applies to access to toilet facilities. Therefore, using 1991 data might overstate the likelihood of control cohorts (those born before the epidemic) having access to piped water and sanitation facilities. In other words, any potential bias introduced by this limitation would likely inflate the placebo effect.

weeks. Tables A3 and A5 present the results under these assumptions. The estimations remain very similar, suggesting that variations in pregnancy length do not materially affect our findings.

8 Concluding Remarks

This paper estimates the effect of prenatal exposure to the Peruvian cholera epidemic on COVID-19 mortality 30 years later. We find that a 1-standard deviation increase in the exposure to cholera in the first trimester in-utero increases Covid mortality by 5% among working-age women. We identify two potential mediators: a biological channel and a behavioral channel. Regarding the biological channel, exposure to cholera during the first trimester in-utero increased cardiovascular vulnerability by 0.04 standard deviations. As for the behavioral channel, cholera exposure during the first trimester in utero increases economic vulnerability by 0.07 standard deviations and has a positive, though not statistically significant, effect on reported COVID-19 cases.

The results of this study highlight the urgent need to intensify global efforts to combat cholera epidemics. Preventative measures are well-established; affluent countries have effectively reduced cholera outbreaks through access to clean drinking water, proper sewage disposal, and vaccination programs. Additionally, this study underscores the necessity of minimizing COVID-19 mortality rates among vulnerable populations. COVID-19 and related epidemics are likely to continue in the future, and many individuals who experienced cholera or other early-life shocks remain at risk. Expanding vaccination outreach could be especially beneficial for these individuals.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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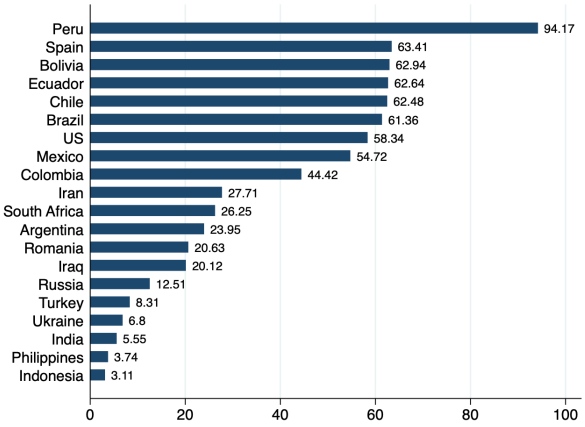
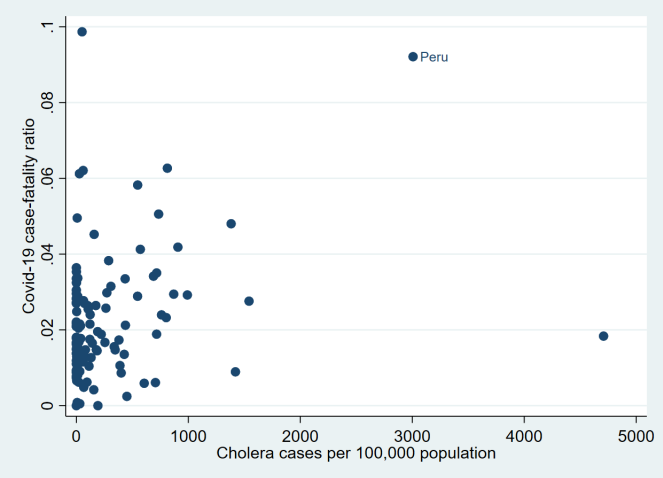
Figure 1: COVID-19 Mortality in the Most Affected Countries - per 100,000 Population



Source: John Hopkins Corona Virus Resource Center. https://coronavirus.jhu.edu/data/mortality

Figure 2: Mortality in the Most Affected Countries - per 100,000 Population



Data Source: World Health Organization. Cholera cases from 1950 to 1995.

Figure 3: Cholera Infection Rate by Region and Month

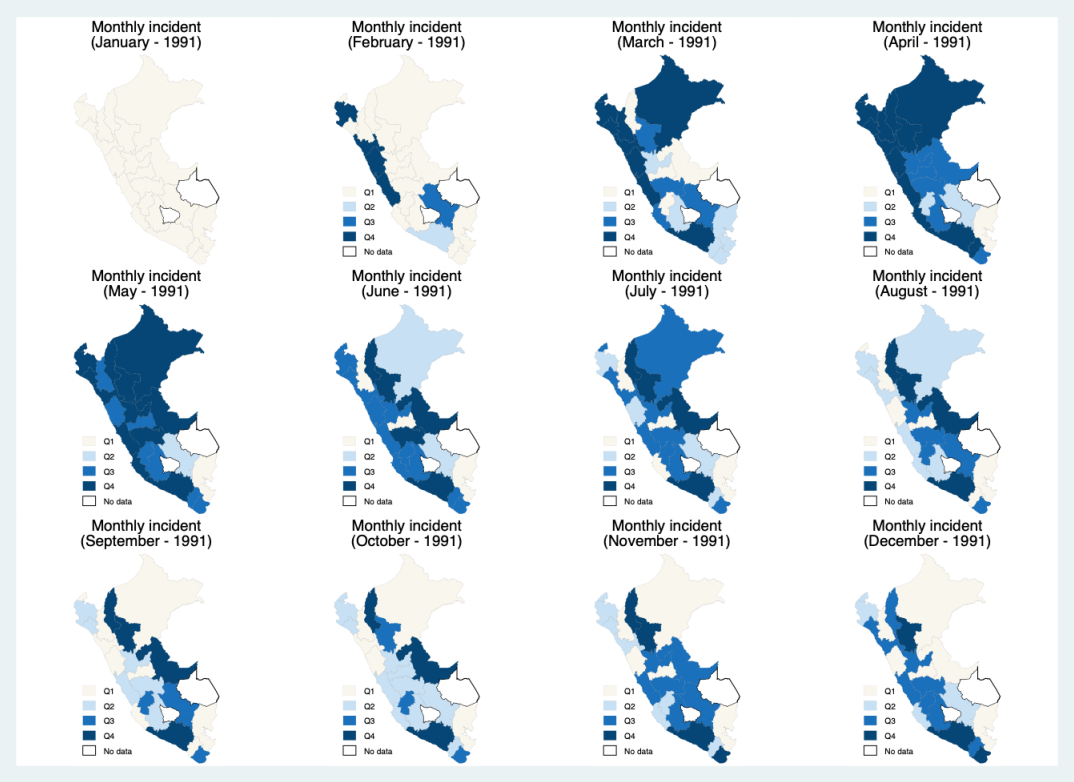


Figure 4: Cholera Incidence by Geographical Region

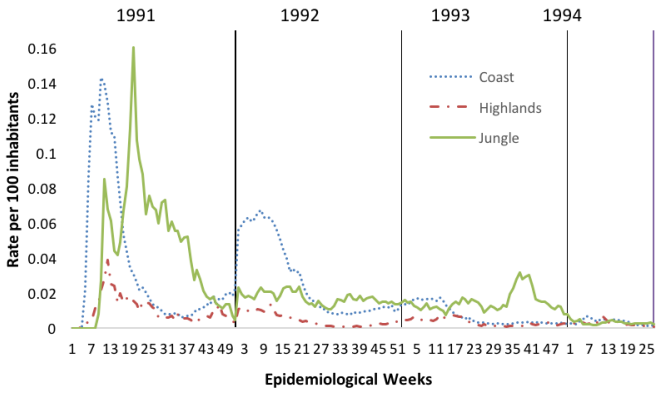


Figure 5: From Cholera to COVID-19 Mortality: Potential Channels

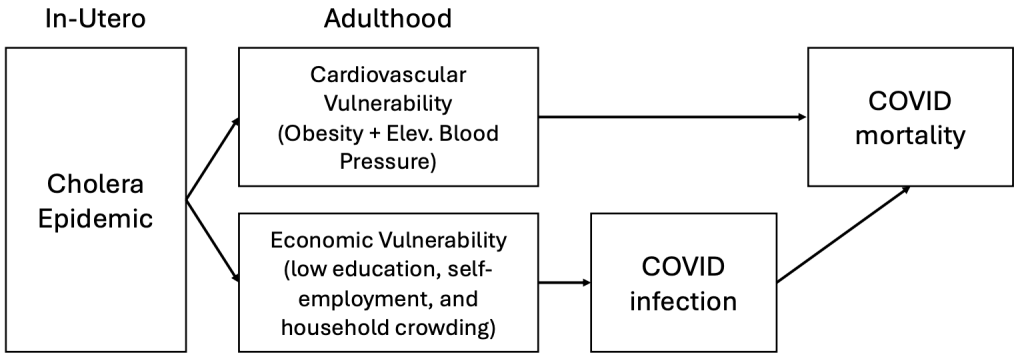


Figure 6: Event Studies by Month of Birth Relative

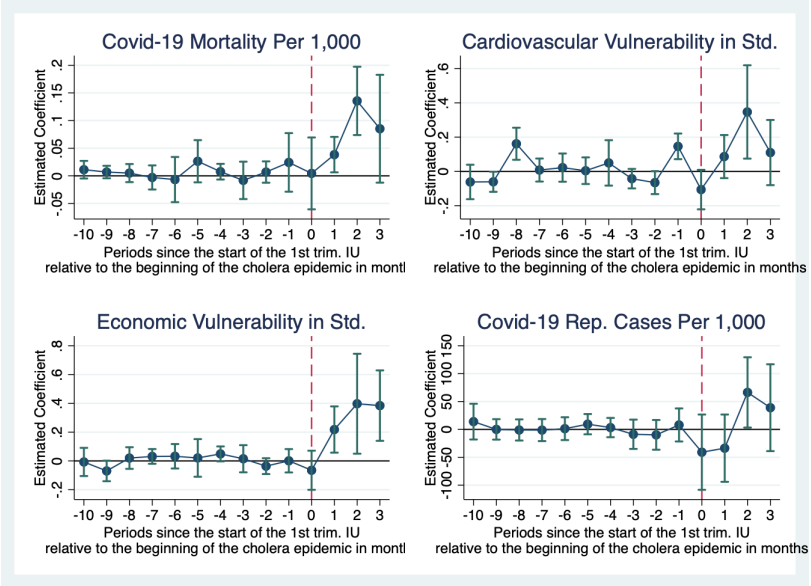


Table 1: Summary Statistics

	Obs.	Mean	Stand. Desv.	Min.	Max.
Covid-19 Mortality Per 1,000	8678	.38	.87	0	31.25
Covid-19 Cases Per 1,000	8678	212.39	289.55	0	1854.84
Cholera Cases 1st trim. IU Per 1,000	120	5.9	6.14	0	32.67
Cardiov. Vulnerability in Std.	8325	0	.79	-1.67	4.74
Obesity Rate Per 100	8646	24.18	12.31	0	100
Elevated Blood Pr. Per 100	8325	29.25	21.31	0	100
Educational Attainment in Years	8649	10.15	2	0	16
Self Employment Per 100	8649	36.15	16.71	0	100
Household Crowding Indiv./bedr.	8649	2.46	.43	.71	12.95
Economic Vulnerability in Std.	8649	0	.78	-3.02	9.36

Table 2: COVID-19 Mortality and Biological Mediators

	(1) Covid-19 Mortality Per 1,000	(2) Cardiovascular Vulnerability in Std.	(3) Obesity Rate Per 100	(4) Elevated Blood Pressure Per 100
Cholera 1st trim. IU (Std)	0.018***	0.037**	0.487***	0.413
	(0.01)	(0.02)	(0.17)	(0.36)
	[0.00]	[0.03]	[0.01]	[0.20]
R^2				
Observations	8678	8325	8646	8325

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table 3: Behavioral Mediators and COVID-19 Reported Cases

	(1) Economic Vulnerability in Std.	(2) Educational Attainment in Years	(3) Self Employment Per 100	(4) Household Crowding Indiv./bedr.	(5) Covid-19 Rep. Cases Per 1,000
Cholera 1st trim. IU (Std)	0.067***	-0.030*	0.635**	0.026***	4.432
	(0.02)	(0.02)	(0.29)	(0.01)	(4.90)
	[0.00]	[0.00]	[0.00]	[0.00]	[0.49]
R^2					
Observations	8649	8649	8649	8649	8678

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table 4: Placebo Effect of Exposure before Conception

	(1) Covid-19 Mortality Per 1,000	(2) Cardiovascular Vulnerability in Std.	(3) Obesity Rate Per 100	(4) Elevated Blood Pressure Per 100
Cholera pre-conception trim. (Std)	0.003	-0.004	-0.004	-0.127
	(0.01)	(0.01)	(0.17)	(0.24)
Cholera 1st trim. IU (Std)	0.019***	0.037**	0.511***	0.356
	(0.01)	(0.02)	(0.17)	(0.35)
R^2				
Observations	8735	8394	8704	8394

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table 5: Placebo Effect of Exposure before Conception

	(1) Economic Vulnerability in Std.	(2) Educational Attainment in Years	(3) Self Employment Per 100	(4) Household Crowding Indiv./bedr.	(5) Covid-19 Rep. Cases Per 1,000
Cholera pre-conception trim. (Std)	-0.015*	0.008	0.155	-0.013***	-5.380
	(0.01)	(0.01)	(0.15)	(0.00)	(4.10)
Cholera 1st trim. IU (Std)	0.063***	-0.035**	0.528*	0.024***	4.108
	(0.02)	(0.02)	(0.29)	(0.01)	(4.90)
R^2					
Observations	8707	8707	8707	8707	8735

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table 6: Placebo Regressions on Mothers

	(1) Number of children	(2) Obesity Rate Per 100	(3) Economic Vulnerability in Std.	(4) Educational Attainment in Years	(5) Piped Water Per 100	(6) Open Defecation Per 100
Cholera 1st trim. IU (Std)	0.021	-0.180	-0.006	0.028	-0.215	-0.010
	(0.04)	(0.46)	(0.02)	(0.05)	(0.84)	(0.01)
	[0.63]	[0.36]	[0.88]	[0.60]	[0.84]	[0.00]
R^2						
Observations	811	811	811	811	811	811

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

A Appendix

Figure A1: Event Studies by Month of Birth Relative

Table A1: Main Outcomes (Aggregated Regions and Cohorts 1987-1992)

	(1) Covid-19 Mortality Per 1,000	(2) Cardiovascular Vulnerability in Std.	(3) Obesity Rate Per 100	(4) Elevated Blood Pressure Per 100
Cholera 1st trim. IU (Std)	0.023*	0.093**	1.135***	-0.140
	(0.01)	(0.04)	(0.31)	(0.68)
	[0.12]	[0.06]	[0.00]	[0.39]
R^2				
Observations	811	811	811	811

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table A2: Main Outcomes (Aggregated Regions and Cohorts 1987-1992)

	(1) Economic Vulnerability in Std.	(2) Educational Attainment in Years	(3) Self Employment Per 100	(4) Household Crowding Indiv./bedr.	(5) Covid-19 Rep. Cases Per 1,000
Cholera 1st trim. IU (Std)	0.142***	-0.051*	0.897*	0.044***	20.277
	(0.04)	(0.03)	(0.49)	(0.01)	(13.40)
	[0.00]	[0.10]	[0.01]	[0.01]	[0.25]
R^2					
Observations	811	811	811	811	811

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table A3: Main Outcomes 36-Week Pregnancy

	(1) Covid-19 Mortality Per 1,000	(2) Cardiovascular Vulnerability in Std.	(3) Obesity Rate Per 100	(4) Elevated Blood Pressure Per 100
Cholera 1st trim. IU- 36w (Std)	0.019***	0.041**	0.496***	0.539
	(0.01)	(0.02)	(0.17)	(0.35)
	[0.00]	[0.01]	[0.02]	[0.17]
R^2				
Observations	8678	8325	8646	8325

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table A4: Main Outcomes 36-Week Pregnancy

	(1) Economic Vulnerability in Std.	(2) Educational Attainment in Years	(3) Self Employment Per 100	(4) Household Crowding Indiv./bedr.	(5) Covid-19 Rep. Cases Per 1,000
Cholera 1st trim. IU- 36w (Std)	0.073***	-0.041**	0.683**	0.027***	6.119
	(0.02)	(0.02)	(0.29)	(0.01)	(4.64)
	[0.00]	[0.00]	[0.00]	[0.00]	[0.50]
R^2					
Observations	8649	8649	8649	8649	8678

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table A5: Main Outcomes 34-Week Pregnancy

	(1) Covid-19 Mortality Per 1,000	(2) Cardiovascular Vulnerability in Std.	(3) Obesity Rate Per 100	(4) Elevated Blood Pressure Per 100
Cholera 1st trim. IU- 34w (Std)	0.016***	0.030*	0.442***	0.248
	(0.01)	(0.02)	(0.17)	(0.36)
	[0.00]	[0.03]	[0.01]	[0.27]
R^2				
Observations	8678	8325	8646	8325

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table A6: Main Outcomes 34-Week Pregnancy

	(1) Economic Vulnerability in Std.	(2) Educational Attainment in Years	(3) Self Employment Per 100	(4) Household Crowding Indiv./bedr.	(5) Covid-19 Rep. Cases Per 1,000
Cholera 1st trim. IU- 34w (Std)	0.056***	-0.018	0.543*	0.024***	2.219
	(0.02)	(0.02)	(0.28)	(0.01)	(5.13)
	[0.00]	[0.31]	[0.00]	[0.00]	[0.47]
R^2					
Observations	8649	8649	8649	8649	8678

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends and control for age, race, temperature, and rainfall. P-values of Wild Bootstrap inferences shown in square parentheses.

Table A7: Main Outcomes (No Controls)

	(1) Covid-19 Mortality Per 1,000	(2) Cardiovascular Vulnerability in Std.	(3) Obesity Rate Per 100	(4) Elevated Blood Pressure Per 100
Cholera 1st trim. IU (Std)	0.019***	0.029**	0.512***	0.380
	(0.01)	(0.01)	(0.16)	(0.38)
	[0.01]	[0.02]	[0.02]	[0.22]
R^2				
Observations	8678	8325	8646	8325

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends. P-values of Wild Bootstrap inferences shown in square parentheses.

Table A8: Main Outcomes (No Controls)

	(1) Economic Vulnerability in Std.	(2) Educational Attainment in Years	(3) Self Employment Per 100	(4) Household Crowding Indiv./bedr.	(5) Covid-19 Rep. Cases Per 1,000
Cholera 1st trim. IU (Std)	0.032***	-0.012	0.533*	0.025***	5.093
	(0.01)	(0.02)	(0.30)	(0.01)	(4.88)
	[0.00]	[0.42]	[0.00]	[0.00]	[0.50]
R^2					
Observations	8649	8649	8649	8649	8678

Note: Regressions include region of residence, month-year of birth fixed effects and region-specific trends. P-values of Wild Bootstrap inferences shown in square parentheses.