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Stillbirth Risk during the 1918 Influenza Pandemic in Arizona, USA.

Smriti Khare

ABSTRACT

Stillbirth Risk during the 1918 Influenza Pandemic in Arizona, USA.

By

SMRITI KHARE

DATE: 12/09/2019

INTRODUCTION: Influenza pandemic of 1918 was the most devastating pandemics to date, affecting approximately one-third of the population worldwide. Prior works have documented the impact of the 1918 influenza pandemic on pregnant mothers and pregnancy outcomes like birth defects, miscarriages or preterm births, but the impact of infection on stillbirth is not studied well.

OBJECTIVE:To assess the stillbirth risk due to the 1918 influenza pandemic in Arizona, USA.

METHODS: We conducted a retrospective study to assess the impact of the 1918 influenza pandemic on stillbirth risk. We manually retrieved 21,334 birth records for the Maricopa County of Arizona state for the years 1915-1925 from a publicly available genealogy database. Logistic regression using SAS statistical software was done to assess the impact of influenza on the risk of stillbirth. Additionally, the study evaluated the risk of stillbirth with advanced maternal age.

RESULTS: The results did not show a significant impact of a pandemic on stillbirth risk. January 1920 experienced the highest rate of stillbirths with 59 stillbirths per 1000 births, 9-10 months later, the deadly second pandemic wave. There was also a higher rate of stillbirth in July 1919, with 49 stillbirths per 1000 births.

Additionally, there was a significant association between stillbirth and advanced maternal age (P-value 0.0096, at 0.05 level of significance) with stillbirth risk of 1.42 (95% Confidence interval: 1.17, 1.72) in younger women (<35 yrs.) compared to older women (≥35 yrs.). The results showed that the risk of stillbirth is least if the age of the mother is approximately 26 years at the time of pregnancy.

DISCUSSION: Though the results did not show a significant impact of the pandemic on stillbirth risk, the study did observe a higher rate of stillbirth in July 1919, consistent with natality decline reported in the previous study in the same month in Arizona. Also, the results are in line with prior work and found that there is a high risk of stillbirths with advanced maternal age.

Stillbirth Risk During the 1918 Influenza Pandemic in Arizona, USA.

by

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Bachelor of Dental Surgery, Barkatullah University, INDIA

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APPROVAL PAGE

STILLBIRTH RISK DURING THE 1918 INFLUENZA PANDEMIC IN ARIZONA, USA

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Author's Statement Page

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SMRITI KHARE

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Chapter I. INTRODUCTION

Influenza is a contagious acute respiratory disease usually caused by the Influenza virus of subtypes A and B (WHO, 2019a). Influenza subtypes A and B are responsible for seasonal flu epidemics every year. There are two proteins on the surface of Influenza A virus: the hemagglutinin (H) and neuraminidase (N) that divide the virus into subtypes, and then it can be further divided into strains(CDC, 2019d). The virus is continually changing and that makes it necessary to update the flu vaccines every year.

According to WHO, 'Influenza pandemic occurs when a new influenza virus emerges and spreads around the world, and most people do not have immunity' (WHO, 2019b). The most recent pandemic occurred in the year 2009 by a novel H1N1 influenza virus, which was believed to exhibit unique combinations of influenza genes not found previously in animals or human beings (CDC, 2019b).

Influenza pandemic is different from seasonal flu, the pandemic is caused by variant of influenza A virus to which people are not immune and spreads rapidly around the globe. Since the pandemic is caused by a new variant of influenza A virus, the vaccinations cannot be prepared ahead of time. A large body of researchers are working on preparing vaccinations in case any predictable variants emerge, but these vaccinations would not be enough to immunize the world population.

Spanish flu or influenza pandemic of 1918 is the deadliest pandemic to date, causing death of estimated 675,000 people in United States and 50-100 million deaths worldwide (Morens & Fauci, 2007). It's been almost 100 years of Influenza pandemic of 1918; the researchers are still trying to understand various aspects of this most disturbing pandemic. The 1918 pandemic was exceptionally severe with a very high case fatality rate compared to other influenza pandemics. As a result of high mortality rate and high case fatality rate the 1918 pandemic was also known as ‘mother of all pandemics’ (Taubenberger & Morens, 2006). The pandemic wiped out one-third of the world population affecting almost 500 million people across the globe(CDC). The 1918 pandemic is believed to be originated in Kansas City, United States, with nearly 100 soldiers ill with flu at a camp in Kansas, the flu then spread across United States, Europe and Asia within six months (CDC, 2019a).

One unique feature of the 1918 pandemic is that it occurred in multiple waves (Sattenspiel et al., 2011). The first wave occurred in early 1918 in the northern part of the hemisphere, with consecutive second and third wave in Fall 1918 and Winter of 1918-1919(Morens & Fauci, 2007). Another salient feature of 1918 pandemic was that unlike other influenza pandemics, the highest mortality was among healthy young adults of age group 20-40 years (Taubenberger et al.,2006, Morens et al., 2007)).

Usually, flu leads to mild respiratory illness that can subside in a week but, flu complications like pneumonia, bronchitis, sinus infections etc. can lead to hospitalization and sometimes death in vulnerable populations(CDC, 2019c). According to WHO, pregnant women, children aged six months to 5 yrs., elderly >65 yrs., and individuals with specific chronic conditions like Asthma and heart conditions, are considered to be at higher risk of complications from the influenza infection(WHO, 2019a).

WHO recommends that pregnant women should be given the highest priority for seasonal flu vaccinations(WHO, 2019a) as they are at elevated risk of complications associated with the influenza infection.

Prior studies have documented the severe effects of influenza among pregnant women. During the 1918 pandemic, 50% of the mortality among women occurred in pregnant women (Harris, 1919). Other severe outcomes of influenza infection on pregnancy includes pregnancy termination, preterm birth (Hardy, Azarowicz, Mannini, Medearis Jr, & Cooke, 1961), low birth weight (Rasmussen, Jamieson, & Uyeki, 2012), etc. Though several studies document the decline in birth rates and early dismissal of fetus, the risk of stillbirth due to influenza virus is still not studied well. Arizona experienced three waves of pandemic with first wave in April/late spring of 1918, second long wave in fall1918-winter1919 and third wave in winter 1920 (Dahal, Jenner, et al., 2018).The study by Dahal et al. provides the evidence of excess mortality in Arizona state due to the 1918 influenza pandemic during the three consecutive waves (Dahal, Jenner, et al., 2018). Our knowledge regarding impact of influenza infection on pregnant women and fetus is improved in recent years but little is known about its effects on stillbirths.

The study aims to assess the impact of 1918 influenza pandemic on the risk of stillbirth in Maricopa county, Arizona state. A study by Dahal et al., shows a decline in birth rates in Arizona after 10 months of the peak in mortality during 1918 influenza in Arizona state, USA(Dahal, Mizumoto, Bolin, Viboud, & Chowell, 2018). This study expects to see a rise in stillbirths during the 1918-1921 influenza pandemic in Maricopa county. Additionally, prior work suggest that risk of stillbirth increases with increase in maternal age, hence this study also attempts to evaluate the risk of stillbirth with advanced maternal age using the publicly available genealogy database.

Chapter II. LITERATURE REVIEW

Influenza pandemic of 1918-1920 also known as ‘Spanish flu’ is the most destructive of all influenza pandemics till date. It is called ‘the mother of all pandemics’ (Taubenberger & Morens, 2006) due to its high global mortality. The pandemic caused approximately 50 million deaths worldwide (Taubenberger & Morens, 2006), and approximately 675,00 deaths in United States (Johnson & Mueller, 2002). Globally it is argued that about one-third of the world population at the time of pandemic was infected by the influenza and had apparent illness (Taubenberger & Morens, 2006). The illness caused by the pandemic flu was extremely severe with a very high case fatality rate of >2.5% compared to <0.1% for other influenza pandemics(Taubenberger & Morens, 2006).

The 1918 pandemic was caused by H1N1 virus, believed to be of avian origin. Taubenberger et al. in his study found that the 1918 virus was of avian source that adapted to humans (Taubenberger et al., 2005). All other influenza pandemics since then are believed to be caused by variants of 1918 influenza virus, hence the named ‘mother of all pandemics’. Taubenberger & Morens in their study mentioned that all the influenza A pandemics since then have been caused by descendants of 1918 virus, including the H2N2(Asian flu) and H3N2(Hong Kong flu) viruses (Taubenberger & Morens, 2006).

One of the most important features of 1918-1919 influenza pandemics, is its high mortality among young adults. Simonsen et al. in their study compared the age distribution related to mortality due to influenza pandemics. They found highest proportion of mortality among people <65 years during 1918 influenza pandemic compared to the later 1957-1958 'Asian Influenza' and 1968-1969 'Hong Kong Influenza' pandemics (Simonsen et al., 1998). Luk et al. found that the 1918-1919 influenza pandemic had peak mortality among young adults (20-40 years) unlike the other Influenza pandemics with a U shaped mortality curve(Luk, Gross, & Thompson, 2001). The Influenza pandemic of 1918-1919 represents a W- shaped mortality curve(Morens & Fauci, 2007), an additional peak for young adults to the usual U shaped curve with peaks for the infants and elderly (Taubenberger & Morens, 2006). A study conducted by Dahal et al. also found excess P&I mortality among individuals of 25-44 years old during the 1918 pandemic (Dahal, Jenner, et al., 2018). Another study conducted in Mexico by Chowell et al., identified elevated mortality in young adults aged 25-44 years, and found a W-shaped curve for mortality during the 1918 Influenza pandemic in Mexico. These results were consistent with the studies conducted in Europe and United States (Chowell, Viboud, Simonsen, Miller, & Acuna-Soto, 2010). Several studies argue about the possible causes behind the disproportionately high mortality among young adults during the 1918-1919 influenza pandemic. Gagnon et al., documents partial immunity among older adults due to the 1889-1890 Russian flu, or excessive immune response among young adults against the infection, or pre-existing disease like pulmonary tuberculosis, or T-cell deregulation(Gagnon et al., 2013).

Another unique feature of Spanish flu is its occurrence in multiple waves. Morens et al. in their study explains the occurrence of 1918 pandemic in three pandemic waves, starting globally in

Spring-Summer 1918 (in northern hemisphere) with consecutive second and third wave in Fall 1918 and Winter of 1918-1919(Morens & Fauci, 2007). According to Taubenberger & Morens the first Spring wave began in March 1918 and spread unevenly across United States, Europe and Asia, the second fall wave occurred between September-November 1918 with simultaneous outbreak across the northern and southern hemisphere, followed by third winter wave in early 1919 (Taubenberger & Morens, 2006). Morbidity was high for the first wave but death rate was low, while the other two waves were highly fatal (Morens & Fauci, 2007).

Though the pandemic ended by summer 1919 in the northern hemisphere, a study conducted in Mexico by Chowell et al. identified a pattern of three successive waves of increased mortality based on age-stratified time series of pneumonia and influenza mortality (Figure 1) in the Mexico city- occurring in Spring (April-May 1918), Autumn (September- December 1918) and Winter (January-April 1920) (Chowell et al., 2010). Another study in Arizona by Dahal et al. recognized three successive pandemic waves in Spring 1918, Fall 1918-Winter1919 and Winter 1920 in Arizona state, United States based on the analysis of mortality records (Figure 11) (Dahal, Jenner, et al., 2018). The influenza pandemic of 1918-1921 killed approximately 0.8% of the total population of Arizona (Dahal, Jenner, et al., 2018).

Pregnant women are susceptible to experience severe complications due to influenza infection based on studies conducted on seasonal influenza epidemics and pandemics (Rasmussen, Jamieson, & Bresee, 2008). Pregnancy leads to immunologic and physiological changes in the body putting them at increased risk of infections and associated complications (Rasmussen et al., 2012). Influenza infection in pregnant women has led to increased mortality, adverse pregnancy outcomes (Harris, 1919)and decline in birth rates (Bloom-Feshbach et al., 2011).

Influenza in pregnant women resulted in the gross mortality of 27% during the 1918-1919 pandemic (Harris, 1919). Cox et al. established that during the influenza season, pregnant women with respiratory illness had significantly longer stay of hospitalization and had higher odds of delivery complications when compared to women without any respiratory illness (Cox et al., 2006).

Influenza infection during pregnancy, with severe illness, can lead to adverse outcomes in the newborns like preterm birth and low birth weight (Rasmussen et al., 2012). Hardy et al, in a study conducted in Baltimore during the 1957-1958 influenza pandemic, concluded that the incidence of premature birth, stillbirth, abortion and congenital malformations are higher in women with influenza infection compared to women without influenza infection (Figure 2) (Hardy et al., 1961). Additionally the authors found that there are significant adverse outcomes like stillbirth, abortion and congenital malformations if the women gets infected in the first trimester (figure 3)(Hardy et al., 1961).

Harris et al, in their study conducted in Maryland, United States found that 50% cases of Influenza infection in pregnant women were complicated by pneumonia, along with interruption of pregnancy in 52% of cases complicated by pneumonia and 27% cases not complicated by pneumonia (Harris, 1919). Also, in cases ending fatally, 62% women went through abortion or premature labor (Harris, 1919). Hardy et al. and Harris at al., both the studies reported higher rates of pregnancy loss/ miscarriages due to exposure to influenza infection during pregnancy, especially during the earliest months of pregnancy.

Several studies mention the decline in birth rate due to the 1918-1919 influenza pandemic. Bloom et al. in a study conducted in Scandinavia and United States experienced a 5-15% decline below baseline in birth rates, by a mean of 2.2 births per 1000 persons in spring 1919 (Bloom-Feshbach et al., 2011). This decline in birth rate in 1919 reached its lowest 6.1-6.8 months after the peak of autumn pandemic; Bloom et al. argue that this depression in natality suggests the that missing births can be due to excess first trimester miscarriages (pregnancy loss) in ~1 in 10 women who were pregnant in autumn 1918 (peak of pandemic) (Bloom-Feshbach et al., 2011). Mamelund in his study examined that the Spanish flu of 1918 caused the decline in conception in 1919 and baby boom in 1920 (Mamelund, 2004). The author in his research concludes that Spanish flu of 1918 caused the baby boom of 1920 in Norway (Mamelund, 2004).

Chandra & Yu, in a study conducted in Taiwan, found a significant decline in birth, nine months after the peak of pandemic mortality (Chandra & Yu, 2015b). Figure 4 demonstrates first trough in seasonally adjusted births 9-10 months (i.e. in August and September 1919) after the first peak mortality of November 1918, followed by second trough 9 months (i.e. in October 1920) after the second peak mortality of January 1920 (Chandra & Yu, 2015b). Another Study by Dahal et al. supports the findings and observed 43% decline in natality in July 1919, after 9-10 months of peak mortality in Arizona (Dahal, Mizumoto, et al., 2018). Figure 5 & 6 display the time series of seasonally and trend adjusted excess death and births for Maricopa County, Arizona between 1915 to 1921 for males and females (Dahal, Mizumoto, et al., 2018). The figure demonstrates troughs in births after 10 months of peak mortality.

Several studies document transplacental transmission of influenza virus and acute illness of mother due to exposure to virus in early pregnancy as probable cause for decline in birth rate, early fetal demise or congenital malformations during the influenza. Yawn et al, in their study recovered influenza virus in maternal tissues, amniotic fluid and fetal heart proving evidence for transplacental transmission of influenza A virus from mother to fetus (Yawn, Pyeatte, Joseph, Eichler, & Garcia-Bunuel, 1971). Another study by Lieberman et al., identified influenza A virus in the maternal and fetal tissues, supporting the passage of virus through placenta (Lieberman, Bagdasarian, Thomas, & Van De Ven, 2011). Lieberman et al., based on evidences of transplacental transmission of virus from mother to fetus, concludes causal relationship between early exposure of influenza infection during pregnancy and fetal death (Lieberman et al., 2011).

In recent years, authors are encouraging Influenza vaccination for pregnant women to prevent mortality, congenital malformations to the infants and prevent early pregnancy loss. Steinhoff et al., in their study conducted on pregnant Bangladeshi women found presence of a high proportion of antibody titer against influenza A vaccine subtypes in immunized mothers and their newborns (Steinhoff et al., 2010). Benowitz et al., in a matched case-control study conducted at Yale-New Haven children's hospital found that in pregnant women immunized with influenza vaccine, the vaccine is 91% effective in preventing hospitalization of infants in the first 6 months of life (Benowitz, Esposito, Gracey, Shapiro, & Vázquez, 2010). Zaman et al., in a randomized controlled trial on Bangladeshi pregnant women found that maternal influenza immunization reduced the laboratory-confirmed influenza illness (Figure 6) by 63% in infants by the age of 6 months (Zaman et al., 2008). Additionally, maternal immunization reduced the severity of influenza infection with a reduction in rate of respiratory illness with fever in newborns(Figure 7&8) and mothers by 29% and 36% respectively (Zaman et al., 2008).

Authors have studied the impact the influenza infection on mortality among pregnant women and early pregnancy loss. If the mother was infected in the first trimester it led to congenital malformations and early abortions/miscarriages. Stillbirths are an important indicator of impact of influenza infection during late pregnancy months. Pierce et al, in a national cohort study conducted in UK, found an increased risk of stillbirths among infants born to mothers infected to 2009 H1N1 influenza virus- There were 27 stillbirths per 1000 live births in infants born to infected mothers compared to 6 stillbirths per 1000 live births in the comparison group (Pierce, Kurinczuk, Spark, Brocklehurst, & Knight, 2011).

Few studies conducted outside United States experienced a rise in stillbirth due to the 1918-1920 Influenza pandemic. Bloom et al., during the 1918 pandemic observed 11.4 excess stillbirths per 1000 live births in Denmark in two months, November 1918 and January 1919 (Bloom-Feshbach et al., 2011). Another study by Bengtsson et al, conducted in Sweden, found a distinct increase in stillbirth rate during the most severe month of pandemic, October 1918 (Bengtsson & Helgertz, 2015). Nishiura et at., documented the Risk ratios for excess stillbirths for two cities in Japan, Kanagawa and Osaka. In Kanagawa, the Risk ratios (RR) were 1.10 (95% CI: 1.08, 1.11) for 1918-1919 and 1.23 (95% CI: 1.21, 1.25) for 1919–1920 (Nishiura, 2009). In Osaka, the RR were 1.30 (95% CI: 1.26,1.33) and 1.24 (95% CI: 1.21, 1.27) for 1919–1920 and 1918-1919 respectively (Nishiura, 2009). In another study conducted in Derbyshire by Reid et al., the infants born during the second and third pandemic waves(July 1918 to April 1919) were 1.247 times more likely to be stillborn than infants born during the period of 1917-1922, with those born during the second wave (September 1918 to January 1919) with 1.535 times more likely to be stillborn (Figure 9) (Reid, 2005). Infants born during the third wave of pandemic were twice as likely to be stillborn than the other times due to maternal ill-health (Reid, 2005). Chandra & Yu observed that death and stillbirths peaked in November 1918 and January 1920 (Figure 10)

(Chandra & Yu, 2015a). Also there was a positive and high contemporaneous correlation between pandemic related stillbirths and excess mortality (Chandra & Yu, 2015a).

Several studies have documented mortality and early pregnancy loss due to influenza infection, but pandemic associated stillbirth risk is not well studied in United States. Dahal et al., documented 43% decline in birth rate in Maricopa County, Arizona (Dahal, Mizumoto, et al., 2018). Our study focuses on stillbirth risk during the pandemic in same study setting.

Since the study is focused on risk of stillbirths, maternal age is believed to be an important indicator of stillbirths. A literature review conducted by Huang et al., observed that in 24 cohort studies and 6 case-control studies, there was a significant association between increased risk of stillbirths and greater maternal age(Huang, Sauve, Birkett, Fergusson, & van Walraven, 2008). The authors found the variation in relative risks from 1.2 to 4.53 for older women compared to younger women, suggesting increased risk of stillbirths in women with advanced maternal age (Huang et al., 2008). In another study, the relative risk of stillbirth was 1.32 (95% confidence interval 1.22, 1.43) and 1.88 (95% confidence interval 1.64, 2.16) for women aged 35 to 39 years old and women 40 years or older when compared to women younger than 35 years old at 37 to 41 weeks of gestation (Reddy, Ko, & Willinger, 2006). The authors concluded that there is a higher risk of stillbirth throughout gestation, with peak risk at 37 to 41 weeks, for women of advanced maternal age.

The present study assesses the impact of 1918 influenza pandemic on risk of stillbirths, and also evaluates the association of stillbirth risk and maternal age.

Chapter III. METHODOLOGY

Study setting:

The study focuses on Maricopa County, Arizona State to assess the risk of stillbirths due to influenza pandemic of 1918. Dahal et al. in their paper documented high mortality in Arizona and decline in birth rates in Maricopa County of Arizona state (Dahal, Jenner, et al., 2018; Dahal, Mizumoto, et al., 2018).

Arizona is a southwestern state, sixth largest and 14th most populous state among the 50 states in the United States(Wikipedia). There were only four states in the United States with a population of American Indians more than 100,000 back in 1990(Passel, 1997). Another distinct feature of Arizona is its dry climate that encouraged many state reports to claim that Arizona's climate is healthy for people with lung disease and tuberculosis, which led to the migration of people with tuberculosis to Arizona, Phoenix in particular (Grineski, Bolin, & Agadjanian, 2006). Maricopa is the largest county in population among the 15 counties in Arizona(Cubit), with Phoenix (Maricopa county) as the largest city in the state(Cubit, 2019). Due to the continued migration of health seekers, TB remained a severe health issue in Arizona through 1950s, which is years after the rate of TB decline in US (Grineski et al., 2006). Maricopa county experienced higher death rates from TB than the rest of Arizona and United States (Grineski et al., 2006).

The influenza pandemic of 1918-1921 killed approximately 0.8% of the total population of Arizona (Dahal, Jenner, et al., 2018). In another study Dahal et al., documented significant decline in natality in Maricopa country 9-10 months after peak pandemic mortality (Dahal, Mizumoto, et al., 2018).

Data Source:

Arizona Genealogy Database (http://genealogy.az.gov/) is generated by the Arizona Department of Health Services. In this database birth records for the years 1855 to 1943 are publicly available. For this study, 21334 birth records for Maricopa county were manually retrieved from this database for January 1915 to December 1925. We entered the birth date, birth status of the child (alive/stillborn/missing), and age of the mother in Microsoft Excel to create a database.

Statistical Analysis:

The statistical analysis was conducted on SAS 9.4 statistical software. The descriptive analysis included the stillbirths categorized according to year and maternal age.

Logistic regression was performed to observe the effect of pandemic on stillbirth risk and to assess the association between maternal age and stillbirth risk.
The models included time as independent variable and maternal age as a covariate. The dependent variable/ outcome was birth status (Alive=1 and stillborn=0), with missing values excluded from the analysis.

To define the pandemic period, we referred to a prior work by Dahal et al., conducted in Arizona to assess the age-specific mortality pattern during the 1918-1921 influenza pandemic in United States. The study identified the period of influenza activity using the time-series of P&I (Pneumonia and influenza) mortality rates (Figure 11) as P&I death rates are the most specific outcome of mortality due to influenza. The study identified the three successive waves of increased mortality- First wave in spring 18 (April 1918), second prolonged wave from fall 1918 (Oct-Dec 1918)- Winter 1919 (Jan-Apr 1919) and third wave in Winter 1920 (Feb-Apr 1920) (Dahal, Jenner, et al., 2018).

The study period from 1915 to 1925 was further categorized as ‘Pre-Pandemic’, ‘Pandemic’ and Post-Pandemic’. Prior work has documented the prolonged influence of the influenza pandemic on the birth outcomes(Chandra & Yu, 2015b), so 9 months were added to the ‘pandemic’ study period to account for the duration of pregnancy (Table1).

Table 1: Classification of study period, from 1915-1925

	Study period category	Time
1.	Pre-Pandemic	January 1915 to March 1918
2.	Pandemic	April 1918 to April 1920 + 9 months*
3.	Post-Pandemic	February 1921 to December 1925

*9 months are added to the pandemic period to account for the duration of pregnancy considering the delayed impact of influenza on birth outcomes.

In this study we assessed the impact of pandemic using logistic regression with time as a categorical independent variable and pre-pandemic period assigned as a reference group. The model included maternal age and quadratic term of maternal age as predictors.

Also logistic regression was ran to evaluate the impact of pandemic on stillbirth risk where time is a continuous independent variable, which was further segmented as Z1 and Z2.
Z1 represents the change of slope from pre-pandemic segment to pandemic segment and Z2 represents the change in slope from pandemic segment to post-pandemic segment. We further tested the beta estimates for Z1 segment to test whether the slope for the pandemic period is zero or not, which further provides evidence if the pandemic period has an effect on risk of stillbirth.

Further, our study estimated the rates of stillbirths per 1000 births for the pandemic period and were plotted for each month from April 1918 to January 1921 (including nine months to account for pregnancy) to observe the pattern of stillbirths during the three consecutive pandemic waves, using the MS EXCEL software.

Additionally, logistic regression analysis was performed to evaluate the association of risk of stillbirth and maternal age(continuous variable). Since the association is non-linear, the model used was-

Logit(P(still Birth))= b_0+b_1 maternal age + b_2(Maternal age)^2

where the quadratic maternal age was used to describe the relationship, and $-b_1/(2b_2)$ gives the maternal age at which the risk of stillbirth is the least if $b_2>0$.

Furthermore, prior literature compared the relative risk of stillbirths in women less than 35 years of age and women 35 or greater than 35 years of age. So our study also evaluated the relative risk of stillbirth for women >=35 years of age compared to women <35 years of age. The maternal age was seperately categorized into two groups, older women(>=35 yrs.) and younger women (<35 yrs.)

Chapter IV. RESULTS

Table 2 shows the total number of still and live births for the years 1915-1925 (study period). The records with missing birth status and missing maternal age were not included in the analysis. Hence 20838 birth records were analyzed of the 21334 birth records retrieved for the study. Table 3 represents the total number of births per year from 1915-1925, with highest birth rate of 12.64% in the year 1920. It also represents the frequency of alive or stillborn year-wise for the study period, with year 1922 and 1917 experiencing the highest and lowest proportion of stillbirths respectively in the study period. For the pandemic period 1918-1920, there was a slight increase in the rate of stillbirths.

Table 4 depicts the four categories of maternal age and the frequency distribution of births for each category. In the study period, 54.29% births occurred among the mothers of age group of 20-29 years, followed by 28.95% births among the age group of 30-39 years. Table 4 also shows that the relationship between stillbirth risk and maternal age is not linear. Mothers of age 40 years and above has the highest percentage of stillborn (3.52%) followed by mothers of age group 30-39 years. The percentage of stillborns is lowest for the mothers of age group 20-29 years.

Taking the continuous maternal age and its quadratic term as predictors, a logistic regression depicts a significant association between stillbirth risk and (maternal age)^2 at 0.05 level of significance (P-value 0.0096).Table 5 represents the beta estimates and p-values for the model.

Model:

Logit(P(still Birth))= b_0+b_1 maternal age + b_2(Maternal age)^2

The results suggest that the rate of stillbirth is lowest when the mother's age is approximately 26 years at the time of pregnancy.

Comparing the risk of stillbirths in women less than 35 years of age and women 35 or greater than 35 years of age, Table 6 represents the 2*2 table of maternal age category (old Vs young) by birth status. The results show a stillbirth risk of 1.42 (95% Confidence interval: 1.17, 1.72) in older women (>=35 yrs.) compared to younger women (<35 yrs.).

Logistic regression was run to assess the impact of pandemic on the risk of stillbirths, Table 7 represents the estimates and P-value for the model, where study period is categorized, with pre-pandemic period as the reference group. Since maternal age has a significant association with the stillbirth risk, maternal age and (Maternal age)^2 are added as covariates to the main model to assess the effect of pandemic on the stillbirth risk. Table 7 also shows the adjusted Odds ratio for the stillbirth risk for pandemic period and 95% Confidence interval.

Also multivariate logistic regression was run to assess the change in slope of the segments that represent the three different pandemic periods. Maternal age and its quadratic term are included as covariates in the model. Time is included as a continuous variable in this model and was divided into segments Z1 and Z2, where Z1 represents the change of slope from pre-pandemic period to pandemic period. Table 8 represents the beta estimates of Z1 and Z2 segments of time and the P-values. The change of slope for the stillbirth risk from pre-pandemic period to pandemic period was not significantly different from zero. Hence, Influenza pandemic from April 1918 to Feb 1921(including 9 months of pregnancy) is not significantly associated with risk of stillbirths, but the relationship with mother's age remains significant.

In this study graph 1 represents the rate of stillbirth for the pandemic period for each month from April 1918 to January 1921. Arizona experienced the deadly second wave of pandemic in the fall of 1918 and winter of 1919. January 1920 represents the highest rate of stillbirths with 59 stillbirths per 1000 births for the pandemic period which is 9 months after the deadly second pandemic wave of winter 1919.

Also, the months of December 1918, October 1920 and January 1921 identified high rate of stillbirths with more than or equal to 50 stillbirths per 1000 births for the respective months. The rate of stillbirths was approximately 50 for December 1918, with 54 and 57 stillbirths per 1000 births for October 1920 and January 1921 respectively (Table 9).

The trend line on graph 1 represents an increasing trend for in the rate of stillbirths per 1000 births for the entire pandemic period from April 1918 to Jan 1921.

Chapter V. DISCUSSION AND CONCLUSION

In this study we assessed the impact of 1918-1920 influenza pandemic on stillbirth risk in Maricopa county, Arizona state. The study expected to find a rise in rate of stillbirths during the pandemic period. We used the same source to retrieve data as prior work done by Dahal et al, in Arizona to assess the mortality pattern and natality decline. The research designated the pandemic waves defined in the previous work by assessing the P&I pandemic mortality in Arizona (Dahal, Jenner, et al., 2018).

The study did not support the hypothesis that the deadly influenza pandemic of 1918 affected pregnancy outcome and caused an increase in the stillbirths. The statistical tests did not find a significant effect of the 1918 influenza pandemic on the stillbirth risk, but we observed a high rate of stillbirths (approximately 59 stillbirths per 1000 live births) in January 1920, which is 9-10 months after the deadly second wave of pandemic in winter 1919 (Jan-Apr). We also observed an increase in the rate of stillbirth, with approximately 50 stillbirths per 1000 births in December of 1918. This peak in stillbirths in our study is to some extent consistent with the rise in stillbirths found in a study conducted by Chandra et al. in Japan, the study found a peak in mortality and stillbirths (figure 10) in January 1920 and November 1918 (Chandra & Yu, 2015a). Though we did not compare the peak in mortality with stillbirths in this study, but we also found an excess rate of stillbirths in July 1919 which is consistent with the natality decline in a prior study conducted in Arizona using the same data.

Dahal et al., in their study conducted in Maricopa County in Arizona state observed a decline in birth rate by 43% in July 1919 (figure 5), 9-10 months after the peak pandemic mortality (Dahal, Mizumoto, et al., 2018). Our study shows a higher rate of stillbirths in July 1919 with approximately 42 stillbirths per 1000 births. The simultaneous decline in birth rates and increase in stillbirths after 9-10 months of peak pandemic mortality can be attributed to influenza infection in mothers during the first trimester of their pregnancies.

Interestingly, our study found a significant association between the age of the mother and risk of stillbirths. Our study is in line with prior work, where there is increased risk of stillbirths for women with advanced maternal age. A systematic review by Huang et al. found that in 24 of 31 cohort studies and all 6 of case-control studies, the risk of stillbirth increased with an increase in maternal age, with a relative risk that varied from 1.2 to 4.3 in older versus younger women (Huang et al., 2008). In our study we found a stillbirth risk of 1.42 in older women compared to women less than 35 years of age. Another study by Reddy et al., documented a higher risk of stillbirth with advanced maternal age, the relative risk of stillbirth was 1.32 and 1.88 for women 35-39 years and women older than 40 years of age respectively, when compared to women less than 35 years of age (Reddy et al., 2006). Additionally, we observed a significant association between stillbirth risk and maternal age (P-value 0.0096) and found that the risk of stillbirth is least when the mother's age is 26 years approximately.

This study is retrospective in design and the birth records are approximately hundred years old, we have many limitations to the study which can explain the lack of correlation. We lack data or information on the health status of the mothers, if the mothers were clinically infected during pregnancy or not. Since Arizona experienced high mortality, hence the study assumes that a higher proportion of pregnant women were infected during the pandemic. Another limitation to the study is the misclassification of birth status on the birth records, since these birth records are images of handwritten birth forms, many records were left blank for Alive/stillborn status by the health care professional in charge. We classified them as alive if the child was named or had an additional record/certificate uploaded for the change of name of the child. This could lead to misclassification and could have underestimated the results.

Additionally, Arizona did not participate in the US vital registration until 1926, the dataset retrieved from genealogy database cannot be compared with the official statistics for the study period for Arizona.

The study employed powerful statistical tools and large sample size to assess the impact of pandemic but many factors could have influenced the pregnancy outcomes like stillbirths, affecting the results. Maricopa especially experienced higher rates of Tuberculosis than rest of the United States (Grineski et al., 2006) until 1950s due to continued migration of people suffering from tuberculosis, because of its dry climate believed to be favorable for treatment of the deadly disease. Our study did not include factors like pre-existing respiratory illness/ tuberculosis that could have potentially led to high stillbirth rate throughout the study period, underestimating the impact of influenza pandemic. Also, our study did not include the effects of factors like socioeconomic status, income, race and ethnicity. Future studies should include demographic and socioeconomic indicators along with laboratory confirmation of influenza infection in mothers.

To conclude, our study did not find significant impact of 1918-1921 influenza pandemic on stillbirth risk. Although the association was not significant, the study did observe peaks in stillbirth rate 9-10 months following the peak in the excess pandemic mortality which could be due to infection in mothers in their first trimester. Additionally, our study is in line with prior literature and observed excess risk of stillbirths with advanced maternal age. The impact of influenza infection on children, elderly and adults have been well studied but we need further work to understand the of impact of influenza infection on pregnant women. This is the first study conducted in Arizona to assess the risk of stillbirths associated with the deadliest pandemic till date. We need further studies to understand the impact of influenza infection since the influenza virus is evolving every year and we need additional public health attention to the vulnerable populations like children, elderly, pregnant women and individuals with severe health conditions.

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APPENDICES

Table 2: Frequency distribution of births (Alive or stillborn)

Birth Status	Frequency	Percent
Alive	20242	97.14
Stillborn	596	2.86
Total	20838	100

Table 3: Table of year from 1915 to 1925 by birth status

Year	Birth Status		
	Alive	Stillborn	Total
1915	1057* 5.07** 96.79***	35 0.17 3.21	1092 5.24
1916	1110 5.33 97.20	32 0.15 2.80	1142 5.48
1917	1247 5.98 97.57	31 0.15 2.43	1278 6.13
1918	1475 7.08 97.10	44 0.21 2.90	1519 7.29
1919	1821 8.74 97.02	56 0.27 2.98	1877 9.01

1920	2553 12.25 96.92	81 0.39 3.08	2634 12.64
1921	2174 10.43 97.23	62 0.30 2.77	2236 10.73
1922	1947 9.34 96.67	67 0.32 3.33	2014 9.67
1923	2075 9.96 97.10	62 0.30 2.90	2137 10.26
1924	2387 11.46 97.39	64 0.31 2.61	2451 11.76
1925	2396 11.50 97.48	62 0.30 2.52	2458 11.80
Total	20242 97.14	596 2.86	20838 100.00

*Frequency
**Percentage
***Row percentage

Table 4: Table of birth status by age group category

Birth Status`	Age group Category				
	10-19 yrs.	20-29 yrs.	30-39 yrs.	40 yrs. and above	Total
Alive	2505* 12.02** 97.02***	11013 52.85 97.35	5846 28.05 96.90	878 4.21 96.48	20242 97.14
Stillborn	77 0.37 2.98	300 1.44 2.65	187 0.90 3.10	32 0.15 3.52	596 2.86
Total	2582 12.39	11313 54.29	6033 28.95	910 4.37	20838 100.00

*Frequency
**Percentage
***Column percentage

Table 5: Logistic regression analysis for the association of stillbirth risk and maternal age

Variable	Beta Estimate	Standard Error	P-Value
Maternal age	-0.10	0.05	0.02*
(Maternal age)^2	0.002	0.00	0.009*

***Significant at 0.05 level of significance

Table 6: Table of Maternal age category (old vs younger women) by birth status

Maternal age category	Birth Status			Relative Risk	95% CI*
	Stillborn	Alive	Total		
Old (>= 35yrs.)	123	3105	3228	**1.42**	**(1.17, 1.72)**
young (< 35 yrs.)(ref)	473	17137	17610		
Total	596	20242	20838		

*Confidence Interval

Table 7: Multivariate analysis for the association of stillbirth risk and time, where time is categorized

Variable	Beta Estimate	Standard Error	P-Value	Adjusted OR (95% CI)
Pandemic period Vs Pre-pandemic period*	0.06	0.12	0.63	1.06 (0.84, 1.35)
Post-pandemic Vs Pre-pandemic period*	-0.07	0.11	0.53	0.93 (0.75, 1.16)
Maternal age	-0.10	0.05	0.02**	
(Maternal age)^2	0.002	0.00	0.009**	

Pre-pandemic period- reference group
**Significant at 0.05 level of significance
OR- odds ratio
CI- confidence interval

Table 8: Multivariate analysis for the association of stillbirth risk and time as a continuous variable

Variable	Beta Estimate	Standard Error	P-Value
Time*	-0.04	0.08	0.59
Z1**	0.11	0.12	0.36
Z2***	-0.13	0.09	0.10
Maternal age	-0.10	0.05	0.02****
(Maternal age)^2	0.001	0.00	0.009****

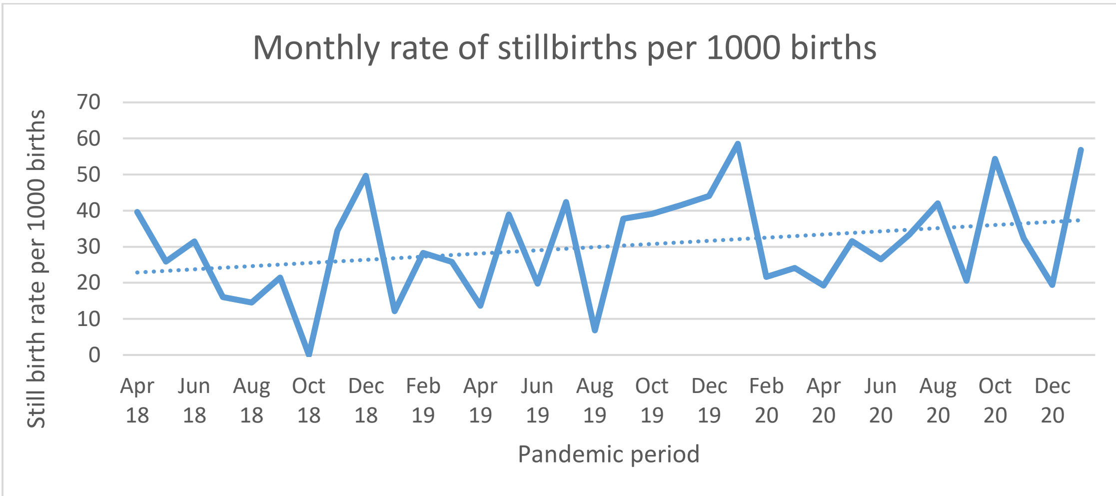
*Time- continuous variable for time period
**Z1 Change of slope from Pre-pandemic to Pandemic period
***Z2 Change of slope from pandemic to post-pandemic period
****Significant at 0.05 level of significance

Table 9: Monthly rate of stillbirths per 1000 births for the pandemic period.

Months	**Rate of stillbirths per 1000 births**
April 1918	39.60
May 1918	25.86
June 1918	31.49
July 1918	16
August 1918	14.50
September 1918	21.43
October 1918	0
November 1918	34.48
December 1918	49.65**
January 1919	12.12
February 1919	28.30
March 1919	25.81
April 1919	13.61
May 1919	38.96
June 1919	19.74
July 1919	42.37
August 1919	6.80
September 1919	37.74
October 1919	39.12
November 1919	41.45
December 1919	44.05
January 1920	58.54*
February 1920	21.62
March 1920	24.15
April 1920	19.23
May 1920	31.53
June 1920	26.55
July 1920	33.33
August 1920	42.06
September 1920	20.58
October 1920	54.39**
November 1920	32.26
December 1920	19.38
January 1921	56.81**

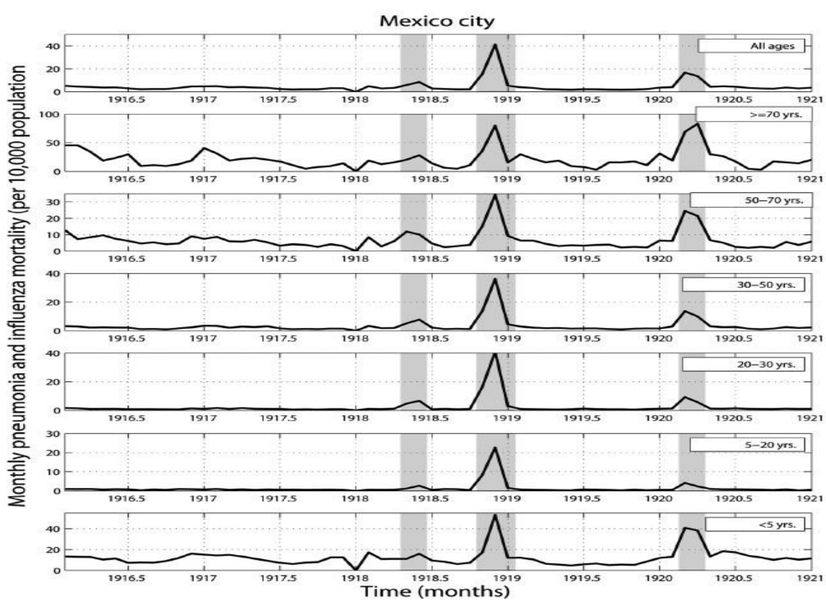
*Highest rate of stillbirth for the pandemic period
** Still birth rate >= 50 stillbirths per 1000 births.

Graph 1: Rate of stillbirths per 1000 births for the pandemic period(Apr 1918- Jan 1921)



The graph shows a trend line that is increasing for the entire pandemic period.

Figure 1: Age-specific monthly time series of pneumonia and influenza mortality rates for Mexico city.



Age-specific monthly time series of pneumonia and influenza mortality rates for Mexico City, 1916–1920. Shaded areas highlight 3 time periods of high mortality associated with 3 waves of the 1918–1920 pandemic occurring in spring (April–May 1918), autumn (October–December 1918), and winter (February–March 1920).

Source: Chowell, G., Viboud, C., Simonsen, L., Miller, M. A., & Acuna-Soto, R. (2010). Mortality patterns associated with the 1918 influenza pandemic in Mexico: evidence for a spring herald wave and lack of preexisting immunity in older populations. *The Journal of infectious diseases, 202*(4), 567-575.

Figure 2: Outcomes of pregnancy in relation to clinical Influenza .

Outcome of Pregnancy in Relation to Clinical Influenza, 611 Pregnancies: 194 White, 417 Negro Patients

	Clinical "Flu," Serologically Confirmed, 332*		No Illness, Serologically "Positive," 206		No Illness, Serologically "Negative," 73	
	No.	%	No.	%	No.	%
Abortion	6	(1.8)	2	(0.9)	0	(0.0)
Stillbirth	8	(2.4)	2	(0.9)	1	(1.3)
Premature	27	(8.0)	20	(9.0)	4	(5.5)
Neonatal death	7	(2.1)	5	(2.4)	2	(2.7)
Neonatal morbidity	29	(8.7)	19	(9.2)	9	(12.3)
Congenital malformation	11	(3.0)	12	(5.9)	1	(1.3)

* Number of individuals in stated category.

Source: Hardy, J. M., Azarowicz, E. N., Mannini, A., Medearis Jr, D. N., & Cooke, R. E. (1961). The effect of Asian influenza on the outcome of pregnancy, Baltimore, 1957-1958. *American Journal of Public Health and the Nations Health, 51*(8), 1182-1188.

Figure 3:Outcome of pregnancy in relation to trimester in which influenza occurred.

Outcome of Pregnancy in Relation to Trimester in Which Influenza Occurred

	First Trimester 75*		Second Trimester 183		Third Trimester 275	
	No.	%	No.	%	No.	%
Abortion	6	(8.0)	3	(1.7)	0	(0.0)
Stillbirth	3	(4.0)	4	(2.1)	4	(1.4)
Premature	10	(13.0)	14	(7.7)	12	(4.3)
Neonatal death	0	(0.0)	2	(1.0)	9	(3.2)
Neonatal morbidity	16	(21.3)	17	(9.2)	30	(10.0)
Congenital malformation	8	(10.7) †	8	(4.3) ‡	7	(2.5) §

* Number of individuals in stated category.

† Three cardiac malformations (one with arthrogryposis), one twin holocardiac monster, three syndactylia, one a large area of hyperpigmentation.

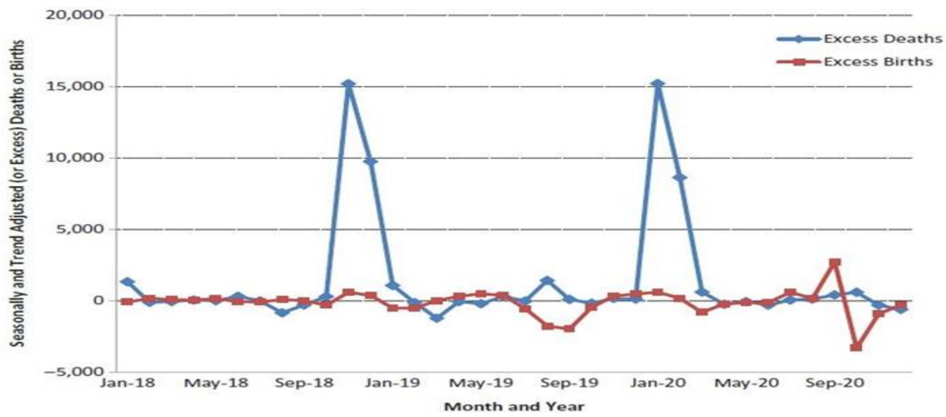
‡ One hip dislocation, one malformed jaw, one multiple malformations, one malformed mouth, three supernumerary digits, one questionable mongoloid.

§ Two cardiac malformations, one club feet, one imperforate anus, one hypospadias, two supernumerary digits.

Note: These malformations were recognized at birth or in the nursery with the exception of two cases found in the review of 19 autopsy protocols, and two cases found during follow-up of 387 children.

Source: Hardy, J. M., Azarowicz, E. N., Mannini, A., Medearis Jr, D. N., & Cooke, R. E. (1961). The effect of Asian influenza on the outcome of pregnancy, Baltimore, 1957-1958. *American Journal of Public Health and the Nations Health, 51*(8), 1182-1188.

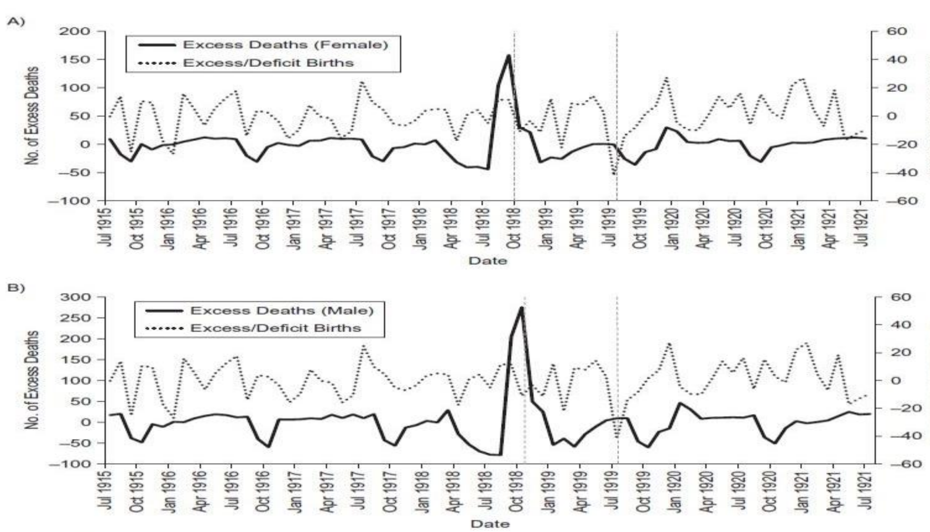
Figure 4: Seasonally and trend-adjusted monthly deaths and births in Taiwan 1918-1920.



Seasonally and trend-adjusted monthly deaths and births in Taiwan, 1918–1920.

Source: Chandra, S., & Yu, Y.-l. (2015b). Fertility decline and the 1918 influenza pandemic in Taiwan. *Biodemography and social biology, 61*(3), 266-272.

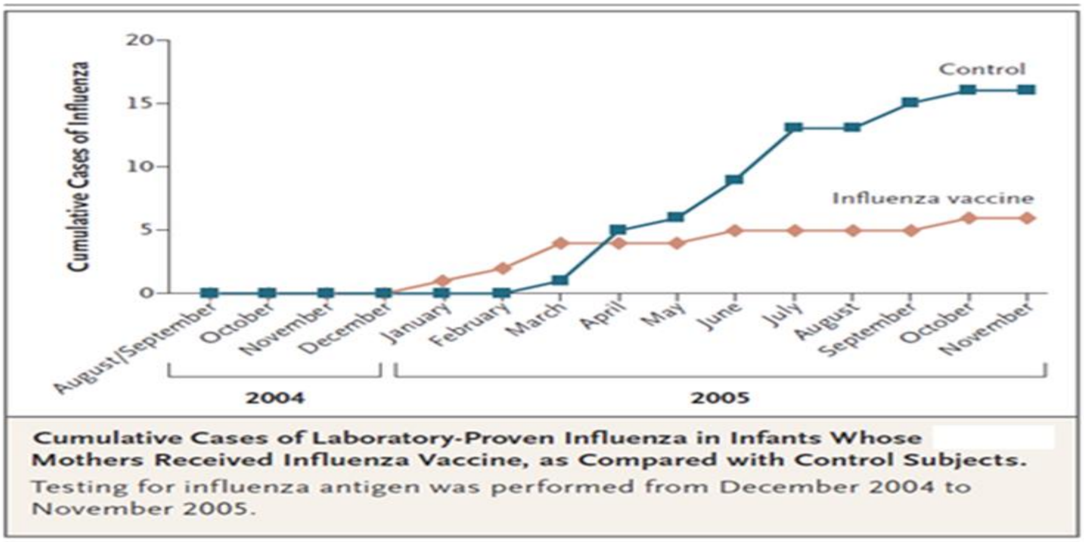
Figure 5: Excess and deficit births and excess Pneumonia and influenza deaths, according to sex, Maricopa County, Arizona, 1915-1921.



Excess and deficit births and excess pneumonia and influenza deaths, according to sex, Maricopa County, Arizona, 1915–1921. Time series of seasonally and trend-adjusted variance in births and excess number of pneumonia and influenza deaths is presented for female (A) and male (B) persons. The vertical dashed lines indicate the timing of peak excess deaths and deficit births, respectively.

Source: Dahal, S., Mizumoto, K., Bolin, B., Viboud, C., & Chowell, G. (2018). Natality decline and spatial variation in excess death rates during the 1918–1920 influenza pandemic in Arizona, United States. *American journal of epidemiology, 187*(12), 2577-2584.

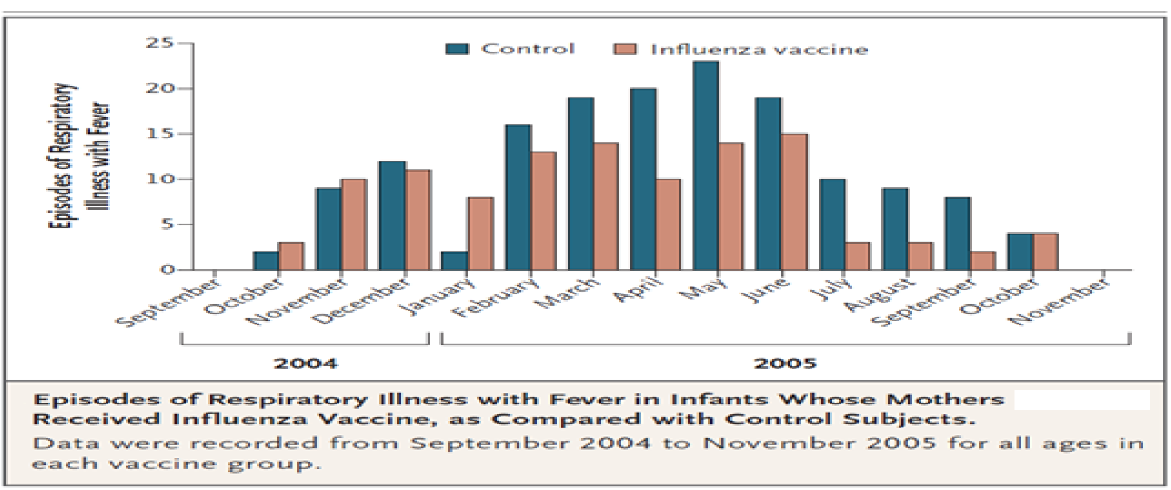
Figure 6: Cumulative cases of Laborartory-proven influenza in infants whose mothers received influenza vaccines compared to control subjects.



Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects. Testing for influenza antigen was performed from December 2004 to November 2005.

Source: Zaman, K., Roy, E., Arifeen, S. E., Rahman, M., Raqib, R., Wilson, E., . . . Steinhoff, M. C. (2008). Effectiveness of maternal influenza immunization in mothers and infants. *New England Journal of Medicine, 359*(15), 1555-1564.

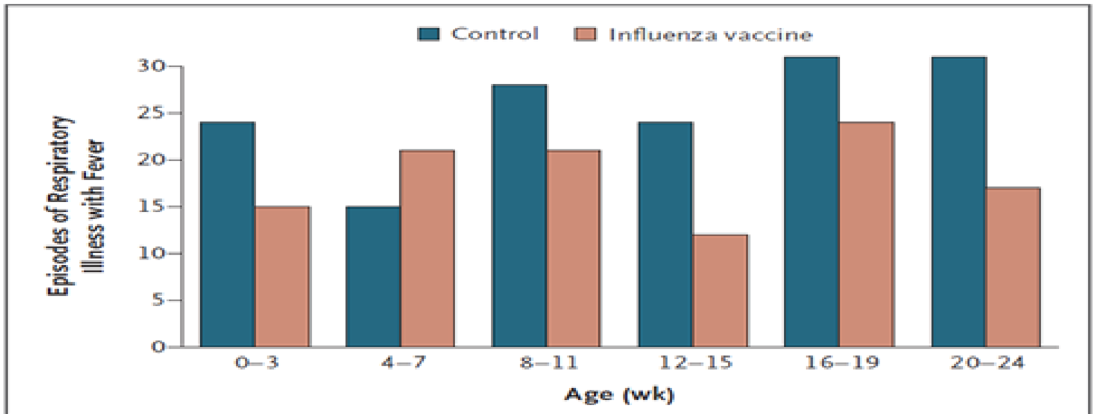
Figure 7: Episodes of respiratory illness with fever in infants whose mothers received influenza vaccine compared to control subjects.



Episodes of Respiratory Illness with Fever in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects. Data were recorded from September 2004 to November 2005 for all ages in each vaccine group.

Source: Zaman, K., Roy, E., Arifeen, S. E., Rahman, M., Raqib, R., Wilson, E., . . . Steinhoff, M. C. (2008). Effectiveness of maternal influenza immunization in mothers and infants. *New England Journal of Medicine, 359*(15), 1555-1564.

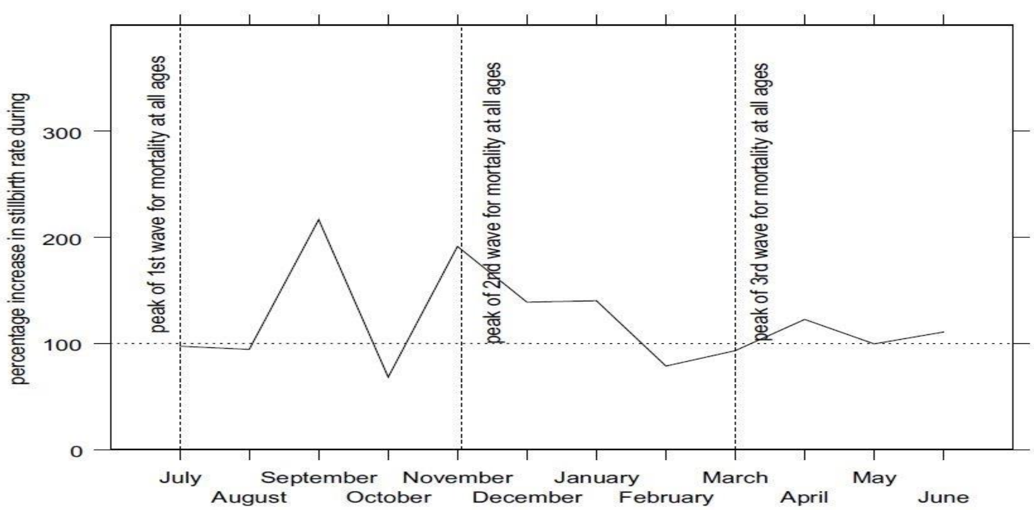
Figure 8: Episodes of respiratory illness with fever in infants whose mothers received influenza vaccine compared to control subjects according to age.



Episodes of Respiratory Illness with Fever in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects, According to Age.

Source: Zaman, K., Roy, E., Arifeen, S. E., Rahman, M., Raqib, R., Wilson, E., . . . Steinhoff, M. C. (2008). Effectiveness of maternal influenza immunization in mothers and infants. *New England Journal of Medicine, 359*(15), 1555-1564.

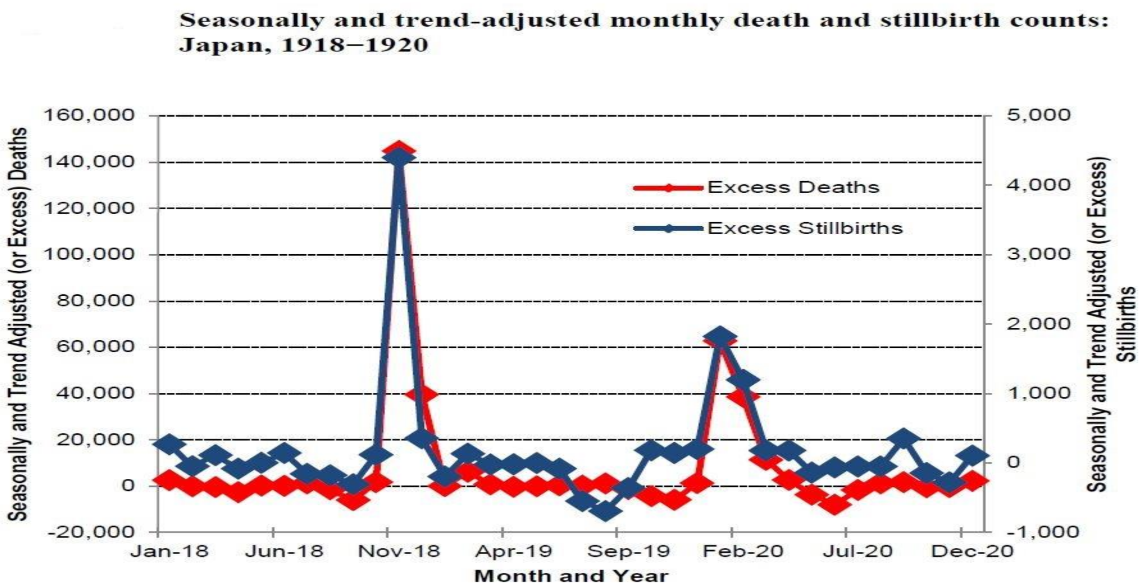
Figure 9:Indexed period stillbirth rates in Derbyshire, late 1918 and early 1919.



Indexed period stillbirth rates in Derbyshire, late 1918 and early 1919 (monthly averages for other years 1917–22 = 100). (Source: Derbyshire health visitor data.)

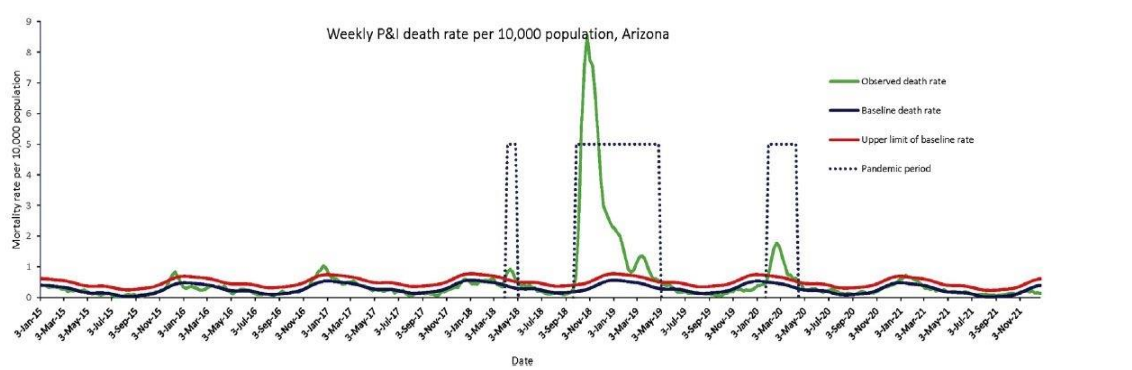
Source: Reid, A. (2005). The effects of the 1918–1919 influenza pandemic on infant and child health in Derbyshire. *Medical History, 49*(1), 29-54.

Figure 10: Seasonally and trend-adjusted monthly death and stillbirth counts: Japan, 1918-1920.



Source: Chandra, S., & Yu, Y.-L. (2015a). The 1918 influenza pandemic and subsequent birth deficit in Japan. *Demographic Research, 33*, 313-326.

Figure 11: Weekly time series of Pneumonia and influenza death rates per 10,000 population in Arizona, 1915-1921.



Weekly time series of P&I death rates per 10,000 population in Arizona, 1915–1921. The green line is the weekly P&I death rates. Dotted lines highlight pandemic waves. The Serfling seasonal regression model baseline (*blue curve*) and corresponding upper limit of the 95% confidence interval of the baseline (*red curve*) are also shown. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Source: Dahal, S., Jenner, M., Dinh, L., Mizumoto, K., Viboud, C., & Chowell, G. (2018). Excess mortality patterns during 1918–1921 influenza pandemic in the state of Arizona, USA. *Annals of epidemiology, 28*(5), 273-280.