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RESEARCH ARTICLE

# Examining the Effect of Parental COVID-19 Vaccination Prior to Birth and the Association Between COVID-19 and Cancer in Children Under Six

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## ABSTRACT

**Introduction:** The biology of COVID-19 has intricate links to childhood cancer, exacerbated by pandemic disturbances. This research aims to explore the association between childhood cancer in children under 6 years old and COVID-19 immunisation, in addition to the effects of vaccination on parents before delivery.

**Method:** The study employs a case-control approach, gathering informed consent and matching factors like age, marital status, and socioeconomic status between cases and controls. A survey was distributed, culminating in 191 children under six, with data from 136 diagnosed cancer cases collected in 2023, adhering to methodological standards in epidemiological research. The analysis utilised SPSS28, employing chi-square testing and logistic regression.

**Result:** Chi-square testing confirmed a significant rise in childhood cancer rates post-COVID-19 pandemic compared to pre-pandemic rates. Key factors influencing cancer incidence include the mother's age at childbirth, parental vaccination history before pregnancy, maternal vaccination details during pregnancy, the child's COVID-19 infection status, and maternal marriage age. Notably, younger mothers faced higher COVID-19 infection risks, but vaccination appears to mitigate paediatric cancer risk.

**Conclusion:** The post-pandemic surge in childhood cancer underscores a complex interplay of early exposures and maternal viral infections. Emphasising vaccination's protective effects before and during pregnancy, the study advocates integrating vaccination into maternal health programs. Public health measures should promote immunisation and address socioeconomic inequalities to lower paediatric cancer risk, aligning with previous studies linking parental health behaviours to childhood cancer incidence.

## 1 | Introduction

Although it is rare, paediatric cancer remains one of the world's most pressing public health issues. In the battle against paediatric cancer, research, enhanced care, and international collaboration are top priorities [1]. Recent trends indicate that advancements in childhood cancer treatments and early detection significantly improve outcomes [2, 3]. Children receiving modern medical care and diagnosed early have a better chance of survival. In low- and middle-income countries,

**Summary**

- A significant increase in childhood cancer incidence has been observed among children under 6 years old in the 4 years following the COVID-19 pandemic.
- The study highlights the association between maternal vaccination, COVID-19 infection status, and paediatric cancer risk, emphasising the need for integrated maternal health programs.
- Maternal and child factors such as younger maternal age at marriage, delayed pregnancies, and parental vaccination history play critical roles in influencing cancer risk.
- Public health initiatives must focus on reducing healthcare disparities and enhancing vaccination outreach to mitigate risks associated with childhood cancer.

healthcare access is restricted, and diagnosis is delayed, leading to poorer prognosis [4–6]. In Iran, over 51,000 cancer cases are diagnosed annually [7]. Paediatric cancers often emerge during public health crises such as COVID-19, as evidenced by global studies attributing delays in treatment and diagnosis to heightened stressors and resource reallocation within healthcare systems [8, 9]. The three most common childhood cancers are leukemia, lymphoma, and central nervous system tumours [10].

Despite certain regions of Iran receiving cutting-edge therapies, rural areas face significant healthcare challenges. Despite government efforts to enhance paediatric oncology care, the burden remains on Iranian families and the healthcare system [11, 12].

The COVID-19 pandemic, which began in late 2019, exacerbated paediatric cancer treatment. Research conducted during this period highlights the vulnerability of paediatric cancer patients to COVID-19 and the resultant disruptions in ongoing treatments [9, 13].

COVID-19 significantly impacts paediatric cancer care as children's immune systems are often compromised [14].

COVID-19, caused by SARS-CoV-2, can spread quickly, overwhelming healthcare systems and necessitating substantial public health responses. Children with complications related to COVID-19 are particularly vulnerable due to their immunocompromised state [15].

Systematic review: the pandemic has led to increased rates of missed cancer diagnoses in children, underscoring the need for stronger health system resilience [9, 16]. In light of the in light of the pandemic, paediatric cancer patients have been investigated due to the complex interactions between treatment delays and concerns about viral exposure. Studies have also assessed the direct effects of COVID-19 on children diagnosed with cancer, focusing on infection susceptibility and illness severity [13].

Understanding the implications of viral infections on childhood cancer processes is a pressing research area [17, 18]. Experts in Iran voiced significant concerns in a pivotal study indicating that new cancer diagnoses in children decreased during the pandemic's peak, indicative of treatment-seeking delays. This could correlate with worse outcomes if diagnoses occur at more advanced stages. Evidence suggests that individuals with cancer who also experience COVID-19 infection face additional complications due to heightened treatment-related issues [19, 20]. This context necessitates paediatric oncology's incorporation of lessons learnt from the COVID-19 experience into future preparedness planning [21, 22]. Cancer care systems must be robust enough to sustain essential services during global health emergencies. Building resilience and innovative approaches are critical for providing timely and effective care for children amid current and future pandemics. The COVID-19 pandemic highlighted the necessity of readiness, flexibility, and comprehensive strategies for vulnerable populations [8, 9]. Recent research has gained substantial attention surrounding maternal immunisation's relevance in supporting maternal and child health outcomes [23, 24]. Given the interplay between COVID-19 and paediatric cancer, it is vital for cancer care systems to ensure essential services even during global health emergencies. Approaching current and future pandemics with innovative strategies is crucial for effectively treating children's health. Insights from the COVID-19 pandemic can enhance paediatric oncology preparedness [25–28].

The process of safeguarding a child's health starts well before birth. Current studies have shown that mothers' immunizations during pregnancy are crucial for protecting both the unborn child and the mother [29]. Vaccinating children against various diseases has become vital to reducing their health risks [25]. Maternal immunisation provides two primary benefits. First, it is the first line of defence against potentially dangerous infections like influenza and pertussis during pregnancy, offering extraordinary protection to unborn infants. Second, the foetus develops passive immunity from maternal antibodies that cross the placenta, benefiting infants in their early months before receiving their vaccinations [25, 29].

This highlights the importance of promoting maternal vaccination as a preventive strategy against potential long-term health outcomes for children [30, 31]. Emerging evidence suggests that maternal vaccinations might indirectly prevent childhood cancers by reducing viral infections associated with the onset of malignancies in later stages [32, 33]. Research indicates that maternal immunizations against hepatitis B and human papillomavirus (HPV) can protect against infections linked to cancer later in life, such as liver or cervical cancer [34].

Furthermore, maternal immunisation substantially decreases the newborn's risk of respiratory infections and other infectious diseases. Early immunological challenges and persistent inflammation can weaken children's immune systems, resulting in serious health issues [35].

The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend numerous vaccinations, including the Tdap vaccine, which covers tetanus, pertussis, diphtheria, and influenza. Studies confirm that vaccinations before pregnancy enhance children's health outcomes post-delivery [25, 36].

The Iranian medical community is increasingly supportive of maternal vaccinations. Vaccine education programs aim to dispel myths and educate pregnant women. High vaccination rates accompany maximum preventive benefits [37, 38].

When mothers are vaccinated, their child's health benefits substantially, providing early illness protection and possibly reducing cancer risks. Recent findings advocate integrating comprehensive prenatal care and maternal immunisation to optimise health outcomes for mothers and children [32–36]. Given the rising concern regarding the long-term effects of COVID-19 and parental vaccinations on children's health, this study seeks to address the following research question: How does parental COVID-19 vaccination before birth, through immunological alterations or indirect epidemiological effects, influence the incidence of childhood cancers in children under 6 years old?

## 2 | Methods

### 2.1 | Study Design

This study utilised a case-control study design, receiving ethical clearance from the Kerman University of Medical Sciences Ethics Committee (reference number IR.KMU.AH.REC.1402.179). Informed consent was obtained from all participants using ethical guidelines that aligned with the best practices highlighted. While matching the case and control groups was conducted based on age, marital status, and economic position, additional confounders such as familial marriages (which may strengthen genetic predisposition), parental comorbidities, parents' education and employment, Mothers' quality of life during pregnancy, and lifestyle factors (e.g., smoking, diet) were controlled for through regression models to minimise bias from these external factors. The case group comprised mothers of children under 6 years old who received a cancer diagnosis at Afzalipour Hospital, Kerman's sole oncology hospital. Data collection focused on mothers of children under six to ensure accurate recall and minimise the influence of ambient and external variables on cancer development in their later children. Out of 20 mothers surveyed about their pregnancy experiences, 19 (90%) reported vivid memories, facilitating accurate recall of their emotions and physical conditions. The remaining 10% could not remember their pregnancies.

According to this information, pregnancy is a particular time for women that facilitates their recollection, and the questions were designed to help them quickly recall their memories. Mothers who found it difficult to remember their experiences during the research were excluded from the analysis. The assignment of participants to the groups remained concealed from the investigators, parallelling the data review process. A questionnaire was randomly distributed to mothers in the oncology department with children under 6 years old. After gathering data from the case group, the same questionnaire was presented to the control group, matched by age, marital status, and neighbourhood. The control group comprised children attending kindergartens and outpatient clinics that do not provide cancer therapy. As of 2023, a total of 136 children under six had received a cancer diagnosis. Data was collected from 73 mothers in the case group, and subsequent data collection from the control group began promptly after that. Seventy-three mothers participated in the case study, with a median economic status score of 8.82 $\pm$ 2.6 and an average age of 35.06 $\pm$ 6.15. After removing outliers, the research comprised 118 mothers. The first control group (Control 1) included 61 mothers with an average age of 34.31 $\pm$ 4.9 years and an economic status score averaging 9.9 $\pm$ 2.6. The second control group (Control 2) comprised 57 mothers, 33.1 $\pm$ 4.96 years of age, and an economic status score averaging 8.81 $\pm$ 2.9. The combined median economic status score for 118 mothers in the control groups was 9.36 $\pm$ 2.8, with an average age of 33.71 $\pm$ 3.91 years.

#### 2.1.1 | Justification of Variables

The selected variables for this study are instrumental in understanding the potential influences on childhood cancer risk:

*Maternal Age at Marriage*: The age at which a mother marries may impact reproductive health and subsequent pregnancy outcomes. Research shows maternal age can correlate with certain health conditions affecting the child's development [8].

*Maternal Age at Childbirth*: Older maternal age at childbirth has been associated with increased risks of genetic abnormalities and other complications. This variable is crucial as it may elucidate any patterns linked to cancer diagnoses in children based on maternal age [39].

*Gender*: Understanding whether there are differences in cancer prevalence between genders helps better target healthcare practices. It can provide valuable insights into risk factors affecting boys or girls [40].

*Child's Age*: This variable is essential since cancer types and incidences vary significantly across different age groups. Identifying any trends within specific age brackets might reveal critical epidemiological data [41].

*Maternal Infection with COVID-19 Before and During Pregnancy*: Given the global COVID-19 pandemic, this variable investigates the impact of maternal health during pregnancy on child outcomes, as viral infections are hypothesised to have potential adverse effects on foetal development [42].

*Maternal COVID-19 Vaccination Before and During Pregnancy*: Assessing vaccination status can identify any protective benefits from maternal vaccinations against infections that may influence the child's health trajectory, including potential immunological repercussions [43].

*Paternal COVID-19 Vaccination Before Mother's Pregnancy*: Since paternal health can influence reproductive health outcomes, this variable examines how paternal vaccination may correlate with childhood health [44].

*Child Infection with COVID-19*: Understanding whether children contracted COVID-19 is vital, as infections could have lasting effects on their health, including the potential for cancer-related conditions [13].

#### 2.1.2 | Sample

To calculate the mean difference between the two independent groups, 190 children under six were included in the sample size calculation for this study. Ultimately, the research comprised 190 children younger than 6 years. Standard statistical techniques for sample size calculations are recommended to ensure robust findings. The study group consisted of Kerman's cancer patients. In 2023, 136 children under six received a cancer diagnosis at the Afzalipour Hospital. Given the case-control nature of this study, the sample size was determined using SPSS28's method for the difference in means between two populations. The power of the study was ensured by accounting for confounding variables in the calculation, while standardized methodologies for case-control designs guided adjustments. To obtain the sample size for the mean difference between two independent groups, employ the formula:

$$n = \frac{\left(z_{1-\frac{a}{2}} + z_{1-B}\right)\left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)}$$

Using SPSS28 for sample size determination necessitates familiarity with the variable's mean under examination in each group. This process aligns with contemporary epidemiological research methodologies. Three studies examined the quality of life among women with healthy and ill children, which were leveraged for data collection.

### 2.2 | Data Analysis

The analysis was utilised using SPSS28, accompanied by visualisation through Microsoft Excel. Both descriptive and analytical statistical techniques were implemented. Given the sample sizes of the case (73) and control groups (118), normality tests (specifically, the Shapiro–Wilk test) were conducted. Differences in means of normally distributed variables between the two groups were compared using the Independent Samples Test. The Mann–Whitney *U* test assessed median differences across groups for non-normally distributed variables. A two-way chi-square test evaluated frequency discrepancies. A multivariable logistic regression model was used to account for confounding variables and determine the odds ratio for the dependent qualitative variable, ensuring adjustments for factors including parental health status and lifestyle. Using these methods, the researchers derived accurate and trustworthy findings from the data.

## 3 | Results

This section delineates the significant findings from our analysis of paediatric cancer incidence among children under 6 years of age before and after the COVID-19 pandemic, linking these trends to maternal health behaviours, demographic factors, and COVID-19 exposure.

### 3.1 | Overview of Cancer Incidence Pre- and Post-COVID-19

As illustrated in Chart 1, the frequency of reported cancer cases in children under 6 years of age has increased significantly during the pandemic years (2020–2023), compared to the pre-pandemic period (2014–2019) (see Table 1). Specifically, results showed that out of 1356 total paediatric cancer cases analysed, 726 were diagnosed during the pre-pandemic period and 630 during the pandemic years (Table 1). The results of our chi-square test confirm that this difference is statistically significant, with a chi-square value of 23.580 and a corresponding *p*-value of 0.0001. This indicates a strong relationship between the COVID-19 pandemic and increased cancer incidence in this demographic.

### 3.2 | Relative Risk of Developing Cancer

Further analysis of relative risk illustrates that children diagnosed with cancer following the pandemic have a 1.584 times higher risk of developing cancer compared to those diagnosed in the pre-pandemic period. This increase in risk is significant, as confirmed by the low *p*-value (0.0001) (Table 2). The

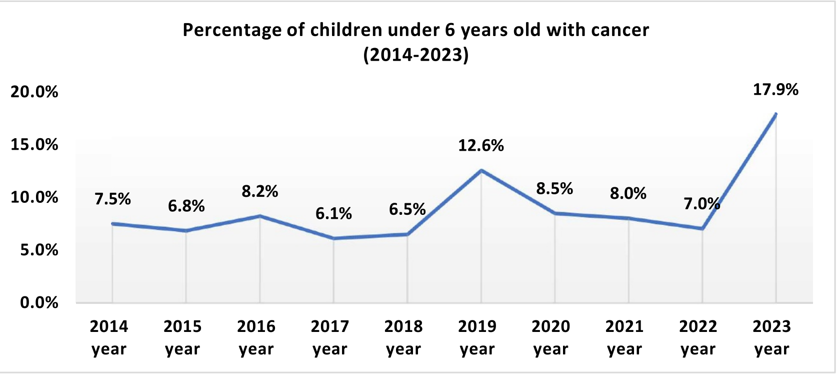


**CHART 1** | Percentage of children with cancer during the years (2014–2023).

confidence interval for this relative risk (1.446–1.735) suggests that one can be confident about the higher likelihood of cancer development in the post-pandemic cohort. However, the variability within this interval indicates that further investigation into potential confounding factors is warranted. Chart 2 presents the comparison of malignant cancer cases in children diagnosed pre- and post-COVID-19, highlighting a significant increase during the pandemic years (2020–2023) (refer to Table 2 for further details).

These findings underscore a critical escalation in both the incidence and severity of cancer in paediatric populations during the pandemic years.

### 3.3 | Analysis of Maternal Characteristics

To better understand the factors contributing to cancer diagnosis, we analysed maternal demographic variables. Notably, the majority of mothers with non-diagnosed children were married between the ages of 24 and 28 years (45.8%), while a significant proportion of mothers of diagnosed children married at or below the age of 18 (28.8%) (Table 3).

The data further reveals that maternal COVID-19 infection rates were elevated among mothers of diagnosed children, with 13.7% reporting infection compared to only 9.3% among non-diagnosed mothers. Vaccination rates also differed sharply, with 95.9% of mothers of diagnosed children being unvaccinated compared to 82.2% of mothers of non-diagnosed children.

### 3.4 | Logistic Regression Analysis of Cancer Risk Factors

In the logistic regression analysis, several maternal and child-related factors emerged as significantly influencing paediatric cancer incidence:

- *Maternal Age at Marriage*: OR = 0.937 (CI = 0.880–0.997), suggesting that marrying at a younger age increases the likelihood of paediatric cancer.
- *Maternal COVID-19 Vaccination*: The OR of 0.268 (CI = 0.088–0.815) indicates a protective role of maternal vaccination against childhood cancer.
- *Child COVID-19 Infection*: Children infected with COVID-19 exhibited over 2.575 times the risk of developing cancer (OR = 2.575, CI = 1.405–4.718).
- *Age of the Child*: There was a significant positive correlation with increasing child age (OR = 1.593, CI = 1.243–2.040)

The following variables were analysed, ordered by significance based on the $\beta$ statistic and $p$-value (Table 4).

- *Maternal infection with COVID-19 before and during pregnancy* (OR = 4.353, CI = 1.299–14.584).
- *Child's COVID-19 infection* (OR = 2.778, CI = 1.347–5.732).
- *Child's age increase* (OR = 1.814, CI = 1.360–2.419).
- *Maternal marriage age below 18 years* (OR = 0.835, CI = 0.757–0.922).

**TABLE 1** | Cancer frequency in children under six before and after the COVID-19 pandemic.

| COVID-19 pandemic | Observed *N* | Expected *N* | Residual | df | Chi-square | *p*-value |
|---|---|---|---|---|---|---|
| Before COVID-19 (2014–2019) | 726 | 813.6 | −87.6 | 1 | 23.580 | 0.0001 |
| COVID-19 years (2020–2023) | 630 | 542.4 | 87.6 | | | |
| Total | 1356 | | | | | |

**TABLE 2** | Comparison of cancer severity in children under six pre- and post-COVID-19 pandemic.

| | Cancer severity | | | | | | Relative risk |
|---|---|---|---|---|---|---|---|
| COVID-19 pandemic | Benign (%) | Malignant (%) | Total | Chi-square | df | *p*-value | 95% CV |
| Before COVID-19 (2014–2019) | 245 (33.7%) | 481 (66.3%) | 726 (100.0%) | 75.148 | 1 | 0.0001 | 1.584 (1.446–1.735) |
| COVID-19 years (2020–2023) | 85 (13.5%) | 545 (86.5%) | 630 (100.0%) | | | | |

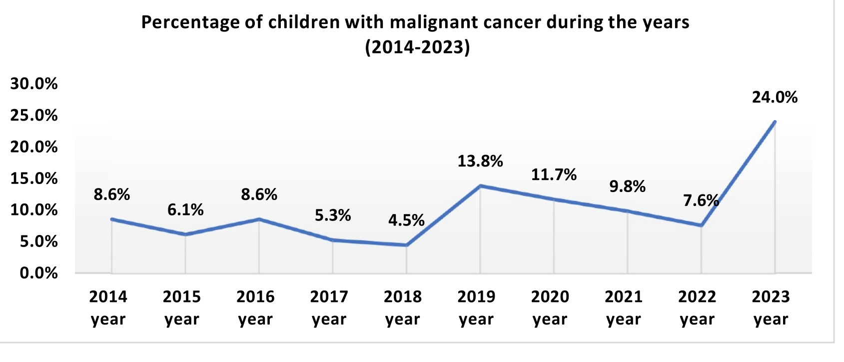


**CHART 2** | Percentage of children with malignant cancer during the years (2014–2023).

**TABLE 3** | Frequency distribution of investigated variables.

| Variables | Not diagnosed with cancer (%) | Diagnosed with cancer (%) |
|---|---|---|
| Maternal age at marriage | | |
| ≤ 18 | 11 (9.3%) | 21 (28.8%) |
| 19–23 | 38 (32.2%) | 28 (38.4%) |
| 24–28 | 54 (45.8%) | 17 (23.3%) |
| 29–33 | 10 (8.5%) | 2 (2.7%) |
| ≤ 24 | 5 (4.2%) | 5 (6.8%) |
| Total | 118 (100%) | 73 (100%) |
| Maternal age at childbirth | | |
| ≥ 18 | (4.2%) 5 | (2.7%) 2 |
| 19–23 | (7.6%) 9 | (8.2%) 6 |
| 24–28 | (30.5%) 36 | (35.6%) 26 |
| 29–33 | (31.4%) 37 | (26%) 19 |
| ≤ 34 | (26.3%) 31 | (27.4%) 20 |
| Total | 118 (100%) | 73 (100%) |
| Gender | | |
| Boy | (53.4%) 63 | (60.3%) 44 |
| Girl | (46.6%) 55 | (39.7%) 29 |
| Total | 118 (100%) | 73 (100%) |
| Child's age | | |
| (1–0) | (12.7%) 15 | (0%) 0 |
| (2–1.1) | (0.8%) 1 | (0%) 0 |
| (3–2.1) | (11%) 13 | (2.7%) 2 |
| (4–3.1) | (14.4%) 17 | (9.6%) 7 |
| (5–4.1) | (23.7%) 28 | (27.4%) 20 |
| (6–5.1) | (37.3%) 44 | (60.3%) 44 |
| Total | 118 (100%) | 73 (100%) |
| Maternal infection with COVID-19 before and during pregnancy | | |
| No | (90.7%) 107 | (86.3%) 63 |
| Yes | (9.3%) 11 | (13.7%) 10 |
| Total | 118 (100%) | 73 (100%) |
| Maternal COVID-19 vaccination before and during pregnancy | | |
| No | (82.2%) 97 | (95.9%) 70 |
| Yes | (17.8%) 21 | (4.1%) 3 |
| Total | 118 (100%) | 73 (100%) |
| Paternal COVID-19 vaccination before mother's pregnancy | | |
| No | (83.1%) 98 | (97.3%) 71 |
| Yes | (16.9%) 20 | (2.7%) 2 |
| Total | 118 (100%) | 73 (100%) |
| A child infection with COVID-19 | | |
| No | (70.3%) 83 | (47.9%) 35 |
| Yes | (29.7%) 35 | (52.1%) 38 |
| Total | 118 (100%) | 73 (100%) |

**TABLE 4** | Logistic regression analysis without interaction effects.

| Variables | | *B* | S.E. | Wald | df | Sig. | Exp(*B*) | 95% C.I. for Exp(*B*) Lower | Upper |
|---|---|---|---|---|---|---|---|---|---|
| Maternal age at marriage | Quantitative numerical variable | −0.065 | 0.032 | 4.196 | 1 | 0.041 | 0.937 | 0.880 | 0.997 |
| | Constant | 1.022 | 0.742 | 1.896 | 1 | 0.169 | 2.779 | | |
| | (≥ 18)* | | | 18.203 | 4 | 0.001 | | | |
| | (19–23) | −0.952 | 0.448 | 4.519 | 1 | 0.034 | 0.386 | 0.160 | 0.928 |
| | (24–28) | −1.802 | 0.465 | 15.049 | 1 | 0.0001 | 0.165 | 0.066 | 0.41 |
| | (2933) | −2.256 | 0.859 | 6.892 | 1 | 0.009 | 0.105 | 0.019 | 0.565 |
| | (≤ 34) | −0.647 | 0.734 | 0.776 | 1 | 0.378 | 0.524 | 0.124 | 2.207 |
| | Constant | 0.647 | 0.372 | 3.018 | 1 | 0.082 | 1.909 | | |
| Maternal age at child's birth | | 0.013 | 0.028 | 0.237 | 1 | 0.626 | 1.014 | 0.960 | 1.07 |
| Constant | | −0.879 | 0.835 | 1.110 | 1 | 0.292 | 0.415 | | |
| Age of the child | | 0.466 | 0.126 | 13.570 | 1 | 0.000 | 1.593 | 1.243 | 2.04 |
| Constant | | −2.696 | 0.642 | 17.617 | 1 | 0.000 | 0.067 | | |
| Gender | Boy* | −0.281 | 0.302 | 0.866 | 1 | 0.352 | 0.755 | 0.418 | 1.365 |
| | Girl | | | | | | | | |
| Constant | | −0.359 | 0.196 | 3.338 | 1 | 0.068 | 0.698 | | |
| Maternal infection with COVID-19 before and during pregnancy | No* | 0.434 | 0.465 | 0.873 | 1 | 0.350 | 1.544 | 0.621 | 3.84 |
| | Yes | | | | | | | | |
| Constant | | −0.530 | 0.159 | 11.126 | 1 | 0.001 | 0.589 | | |
| A child infected with COVID-19 | No* | 0.946 | 0.309 | 9.365 | 1 | 0.002 | 2.575 | 1.405 | 4.718 |
| | Yes | | | | | | | | |
| Constant | | −0.863 | 0.202 | 18.356 | 1 | 0.000 | 0.422 | | |
| Maternal COVID-19 vaccination before and during pregnancy | No* | −1.318 | 0.568 | 5.385 | 1 | 0.02 | 0.268 | 0.088 | 0.815 |
| | Yes | | | | | | | | |
| Constant | | −0.341 | 0.157 | 4.677 | 1 | 0.031 | 0.711 | | |
| Paternal COVID-19 vaccination before Mother's pregnancy | No* | −1.98 | 0.758 | 6.829 | 1 | 0.009 | 0.138 | 0.031 | 0.61 |
| | Yes | | | | | | | | |
| Constant | | −0.322 | 0.156 | 4.276 | 1 | 0.039 | 0.724 | | |

*Note:* The * symbol denotes the reference group coded as 1 in the logistic regression analysis.

- *Maternal age increase at childbirth* (OR = 1.092, CI = 1.009–1.181).

These results suggest that maternal age under 18, along with increased maternal age at childbirth, elevates the likelihood of childhood cancer due to associated delays in pregnancy (Table 5).

### 3.5 | Implications of Findings

These analyses provide compelling evidence of the multifactorial nature of paediatric cancer risk in the context of the COVID-19 pandemic. Variability in maternal age at marriage, vaccination status, and direct exposure to COVID-19 have been identified as significant contributors to increased risk, highlighting critical areas for public health interventions.

### 3.6 | Conclusion

In summary, the findings from this study illustrate a substantial increase in paediatric cancer cases correlating with the COVID-19 pandemic, driven by various maternal and child health factors. Continuous monitoring and focused public health initiatives are essential to mitigate these risks moving forward.

## 4 | Discussion

Notably, there has been a significant increase in the incidence of paediatric cancer among children under 6 years old in the 4 years after the COVID-19 pandemic (2020–2023). The epidemic has caused notable increases in both leukaemic and malignant malignancies [19, 20]. Potential factors driving this increase include delayed medical diagnoses, heightened stress, and

**TABLE 5** | Logistic regression analysis accounting for group variable interaction effect.

| Variables | | *B* | S.E. | Wald | df | Sig. | Exp(*B*) | 95% C.I. for Exp(*B*) Lower | 95% C.I. for Exp(*B*) Upper |
|---|---|---|---|---|---|---|---|---|---|
| Maternal age at marriage | | −0.180 | 0.050 | 12.766 | 1 | 0.000 | 0.835 | 0.757 | 0.922 |
| Maternal age at child's birth | | 0.088 | 0.040 | 4.748 | 1 | 0.029 | 1.092 | 1.009 | 1.181 |
| Age of the child | | 0.596 | 0.147 | 16.428 | 1 | 0.000 | 1.814 | 1.360 | 2.419 |
| A child infected with COVID-19 | | 1.022 | 0.370 | 7.647 | 1 | 0.006 | 2.778 | 1.347 | 5.732 |
| Maternal infected with COVID-19 before and during pregnancy | No* | 1.471 | 0.617 | 5.684 | 1 | 0.017 | 4.353 | 1.299 | 14.584 |
| | Yes | | | | | | | | |
| Constant | | −2.376 | 1.194 | 3.958 | 1 | 0.047 | 0.093 | | |

*Note:* The * symbol denotes the reference group coded as 1 in the logistic regression analysis.

significant changes to environmental conditions. It is essential to consider alternative explanations, such as advancements in diagnostic technology or emerging health trends. Continued research indicates that social determinants of health play a pivotal role in shaping health outcomes, warranting a multidisciplinary approach to identify specific causes and targeted solutions [4–6, 8, 9]. This is particularly critical in low-resource settings where healthcare disparities manifest more markedly and access to early diagnostics is limited. Public health policies should emphasise equitable healthcare access to minimise delays in diagnosis, which could lead to advanced stages of paediatric cancer within underserved populations.

Broader public health strategies addressing socioeconomic inequalities should be part of a comprehensive approach aimed at lowering childhood cancer incidence. By integrating these more comprehensive strategies, public health efforts can effectively target vulnerable communities [4–6, 45]. These guidelines must be more specific and actionable to enhance the impact and applicability of public health recommendations. This specificity ensures that strategies are theoretical, practically feasible, and tailored to the needs of communities. By delineating clear steps for implementation, such as targeted vaccination campaigns, educational outreach on maternal health, and strategies to enhance healthcare access, public health policies can make a far more compelling case for addressing the increasing incidence of paediatric cancer. Such detailed guidelines will empower healthcare practitioners and policymakers to take informed actions that can lead to tangible improvements in child health outcomes.

This need for systematic health planning directly confronts existing inequalities, particularly in resource-scarce environments where diagnostic and vaccine access limitations exacerbate health outcomes. Understanding the factors contributing to this increasing trend and promoting effective prevention and treatment strategies requires urgent attention and further research [45]. Findings from the univariate logistic regression analysis pin down various factors influencing childhood cancer incidence. Complicated interactions dictate the incidence of childhood cancer, where maternal and paternal COVID-19 vaccination status, maternal and child COVID-19 infection, and increasing child age intertwine with environmental risk factors [13, 41–44]. Findings from this study have immediate relevance for healthcare planners working in low-resource environments. The pressing necessity for comprehensive vaccination programs that reach marginalised populations cannot be overstated. By enhancing vaccination rates among parents, healthcare systems can simultaneously address infectious and non-communicable diseases in at-risk groups, thus narrowing healthcare disparities.

Maternal vaccination's function as a preventive measure extends beyond infectious diseases, potentially defending against paediatric cancer-promoting risks faced by infants and young children [29, 32–36].

These findings have implications that emphasise the need to integrate maternal vaccination strategies into broader public health initiatives aimed at infectious disease prevention and long-term health risks like cancer. Public health policymakers should prioritise awareness campaigns surrounding the dual advantages of maternal vaccinations.

Understanding these associations is essential for creating effective prevention strategies to reduce childhood cancer burdens. Future studies should concentrate on maternal vaccination interventions that can significantly improve child health outcomes [45, 46].

This highlights how immunizations are crucial for preventing infectious illnesses and lowering the incidence of paediatric cancer. Immunizations can protect against viral infections that could harm a developing foetus by fortifying the immune systems of both parents. Moreover, a good perinatal environment is necessary to reduce the incidence of certain childhood-associated cancers [43, 44].

In the broader public health context, findings emphasise the criticality of policymakers in designing comprehensive strategies bridging maternal health interventions with childhood cancer prevention. Insights into these interfaces will facilitate the development of a more potent approach to alleviate adverse outcomes stemming from maternal viral infections. Marriages occurring under the age of 18 and older maternal age at childbirth are linked to heightened cancer risks in offspring [8, 39]. However, it's equally important to examine other competing factors such as socioeconomic conditions, access to healthcare, and environmental contributing factors, all of which significantly shape cancer outcomes [47, 48].

To effectively address the intricate nature of paediatric cancer, integrated solutions must surpass individual risk factors, directly targeting systemic roots through public health strategies.

Recognising the complexity of these dynamics is pivotal to designing thorough preventive and intervention frameworks. By identifying various contributors to paediatric cancer risk, healthcare practitioners and policymakers can implement tailored interventions to modify risk factors and enhance health outcomes for affected children.

Policymakers should prioritise resource allocation for community-level interventions addressing environmental and socioeconomic health determinants to mitigate paediatric cancer risk.

### 4.1 | Limitations

Although the case-control design facilitated reliable comparisons, the lack of longitudinal data restricts the ability to establish definitive causal relationships between parental health behaviours, specifically vaccination, and childhood cancer risk. Despite improvements in understanding the association between parental COVID-19 vaccination and paediatric cancer incidence, the study still lacks depth in longitudinal analysis. This limitation significantly hinders our ability to infer causality, as cross-sectional observations do not provide insight into the temporal relationships between vaccinations, COVID-19 exposure, and subsequent cancer development in children. Longitudinal studies allow for tracking these variables over time and help discern whether parental vaccination genuinely influences the incidence of childhood cancers or if other confounding factors are at play. More detailed recommendations for future research could include employing a longitudinal approach that monitors children's health outcomes over several years following maternal vaccination and COVID-19 exposure. Such studies could significantly enhance the robustness of findings and provide more apparent evidence regarding the protective effects of vaccinations and the long-term impact of COVID-19 on childhood health.

The increase in paediatric cancer incidence following the COVID-19 pandemic is influenced by complicated interactions that include maternal and paternal COVID-19 vaccination status, maternal and child COVID-19 infection, and increasing child age intertwined with environmental risk factors [13, 41–44]. This necessitates caution in interpreting results, as the relationship between these factors and paediatric cancer risk is multifaceted. While there is evidence supporting the beneficial effects of maternal vaccination on child health [32–36], some researchers argue that there is insufficient evidence linking maternal vaccination directly to reductions in paediatric cancer rates [49, 50].

Furthermore, various health determinants—including socioeconomic status, access to healthcare, and environmental factors—significantly shape cancer outcomes [47, 48]. The challenges of early marriages and delayed motherhood also intensify risks, highlighting the importance of investigating these elements [8, 39]. Understanding the intricate connections between these demographic variables and childhood cancer risk is vital for crafting targeted interventions aimed at modifiable risk factors that can improve outcomes.

This emphasises the need for research to scrutinise further links between maternal health, childhood outcomes, and paediatric cancer risks [48].

Additionally, while vaccinations are essential for preventing infectious diseases and may potentially reduce paediatric cancer incidence, discrepancies in their impact warrant further examination [47, 48], recognition of how systemic roots of health disparities contribute to the rising paediatric cancer incidence is critical, necessitating comprehensive strategies that go beyond individual risk factors [25–27].

## 5 | Conclusion

A significant rise in paediatric cancer incidence among children under 6 years of age has occurred in the 4 years following the COVID-19 pandemic. Vaccination before and during pregnancy emerges as a pivotal measure for preventing paediatric cancer, underscoring the vital role of integrating maternal health strategies within broader public health frameworks.

Younger maternal age at marriage and Delayed pregnancy, along with COVID-19 infections in mothers and children, correlate with increased cancer risks. Public health approaches should focus on mitigating healthcare inequalities and enhancing vaccination outreach. By bridging gaps in access to preventive healthcare services, particularly immunizations, health systems can more effectively manage and lower the risks of childhood cancers.

Further research is needed to advance children's health outcomes and elucidate the underlying mechanisms driving these associations during global health emergencies like COVID-19. Preventive strategies and targeted treatments should be designed to address modifiable risk factors to reduce paediatric cancer incidence. Developing sustainable public health strategies that link maternal health, vaccination, and childhood cancer prevention is paramount for those in resource-strapped environments.

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#### Ethics Statement

Ethics approval for this study was obtained from the University of Medical Sciences ethics committee (approval number: IR.KMU.AH.REC.1402.179).

## Consent

Comprehensive informed consent was obtained in this study in accordance with established procedures. Patients were provided with detailed information about the study's purpose and were assured of confidentiality.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## References


1. I. Astigarraga, "Advances and Challenges in the Fight Against Childhood Cancer," *Anales de Pediatía* 82, no. 2 (February 2015): 57–58, Avances y retos en la lucha contra el cáncer infantil, https://doi.org/10.1016/j.anpedi.2014.11.001.

2. T. J. Ohlsen, M. R. Martos, and D. S. Hawkins, "Recent Advances in the Treatment of Childhood Cancers," *Current Opinion in Pediatrics* 36, no. 1 (2024): 57–63, https://doi.org/10.1097/mop.0000000000001310.

3. E. Butler, K. Ludwig, H. L. Pacenta, L. J. Klesse, T. C. Watt, and T. W. Laetsch, "Recent Progress in the Treatment of Cancer in Children," *CA: A Cancer Journal for Clinicians* 71, no. 4 (2021): 315–332, https://doi.org/10.3322/caac.21665.

4. J. Lubega, R. L. Kimutai, and M. M. Chintagumpala, "Global Health Disparities in Childhood Cancers," *Current Opinion in Pediatrics* 33, no. 1 (2021): 33–39, https://doi.org/10.1097/mop.0000000000000984.

5. W. Zabih, A. B. Thota, G. Mbah, P. Freccero, S. Gupta, and A. E. Denburg, "Interventions to Improve Early Detection of Childhood Cancer in Low- and Middle-Income Countries: A Systematic Review," *Pediatric Blood and Cancer* 67, no. 12 (2020): e28761, https://doi.org/10.1002/pbc.28761.

6. I. Magrath, E. Steliarova-Foucher, S. Epelman, et al., "Paediatric Cancer in Low-Income and Middle-Income Countries," *Lancet Oncology* 14, no. 3 (2013): e104–e116, https://doi.org/10.1016/s1470-2045(13)70008-1.

7. S. Alireza, N. Mehdi, M. Ali, M. Alireza, M. Reza, and D. Parkin, "Cancer Occurrence in Iran in 2002, an International Perspective," *Asian Pacific Journal of Cancer Prevention* 6, no. 3 (2005): 359.

8. M. Dvori, S. Elitzur, A. Barg, et al., "Delayed Diagnosis and Treatment of Children With Cancer During the COVID-19 Pandemic," *International Journal of Clinical Oncology* 26, no. 8 (2021): 1569–1574, https://doi.org/10.1007/s10147-021-01971-3.

9. A. Majeed, T. Wright, B. Guo, R. S. Arora, C. G. Lam, and A. L. Martiniuk, "The Global Impact of COVID-19 on Childhood Cancer Outcomes and Care Delivery –A Systematic Review," *Frontiers in Oncology* 12 (2022): 869752, https://doi.org/10.3389/fonc.2022.869752.

10. S. M. Mousavi, A. Pourfeizi, and S. Dastgiri, "Childhood Cancer in Iran," *Journal of Pediatric Hematology/Oncology* 32, no. 5 (2010): 376–382, https://doi.org/10.1097/mph.0b013e3181e003f7.

11. S. Khazaei, E. Ayubi, M. Soheylizad, and K. Manosri, "Incidence Rate and Distribution of Common Cancers Among Iranian Children," *Middle East Journal of Cancer* 8, no. 1 (2017): 39–42.

12. N. Rezaei, F. Pishgar, M. Yoosefi, et al., "National and Sub-National Pediatric Cancer Mortality in Iran, 2000–2015," *Archives of Iranian Medicine* 22, no. 6 (2019): 293–300.

13. A. R. Kahn, C. M. Schwalm, J. A. Wolfson, J. M. Levine, and E. E. Johnston, "COVID-19 in Children With Cancer," *Current Oncology Reports* 24, no. 3 (2022): 295–302, https://doi.org/10.1007/s11912-022-01207-1.

14. E. R. Sniderman, D. E. Graetz, A. Agulnik, et al., "Impact of the COVID-19 Pandemic on Pediatric Oncology Providers Globally: A Mixed-Methods Study," *Cancer* 128, no. 7 (2022): 1493–1502, https://doi.org/10.1002/cncr.34090.

15. D. C. Moreira, G. C. Millen, S. Sands, P. R. Kearns, and D. S. Hawkins, "The Care of Children With Cancer During the COVID-19 Pandemic," *American Society of Clinical Oncology Educational Book*, 41 (2021): 1–10, https://doi.org/10.1200/edbk_321497.

16. F. Boiardi and J. Stebbing, "Developments in Paediatric Cancer Care Throughout the COVID-19 Pandemic: Lessons From China," *Lancet Regional Health–Western Pacific* 20 (2022): 100398, https://doi.org/10.1016/j.lanwpc.2022.100398.

17. M. E. McLaughlin-Drubin and K. Munger, "Viruses Associated With Human Cancer," *Biochimica et Biophysica Acta – Molecular Basis of Disease* 1782, no. 3 (2008): 127–150, https://doi.org/10.1016/j.bbadis.2007.12.005.

18. K. Alibek, A. Mussabekova, A. Kakpenova, et al., "Childhood Cancers: What Is a Possible Role of Infectious Agents?," *Infectious Agents and Cancer* 8 (2013): 1–9, https://doi.org/10.1186/1750-9378-8-48.

19. S. Sinha and C. N. Kundu, "Cancer and COVID-19: Why Are Cancer Patients More Susceptible to COVID-19?," *Medical Oncology* 38, no. 9 (2021): 101, https://doi.org/10.1007/s12032-021-01553-3.

20. Z. Bakouny, J. E. Hawley, T. K. Choueiri, et al., "COVID-19 and Cancer: Current Challenges and Perspectives," *Cancer Cell* 38, no. 5 (2020): 629–646, https://doi.org/10.1016/j.ccell.2020.09.018.

21. V. Szenes, R. Bright, D. Diotallevi, et al., "Stepwise Strategic Mitigation Planning in a Pediatric Oncology Center During the COVID-19 Pandemic," *Journal of Pediatric Oncology Nursing* 38, no. 3 (2021): 176–184, https://doi.org/10.1177/1043454221992301.

22. G. K. Katato, P. Sitaula, A. Gupte, and E. T. Al-Antary, "The Impact of COVID-19 on Pediatric Malignancy Diagnosis and Treatment: Never the Same but Lessons Learned," *Vaccines* 11, no. 3 (2023): 667, https://doi.org/10.3390/vaccines11030667.

23. B. Lindsey, B. Kampmann, and C. Jones, "Maternal Immunization as a Strategy to Decrease Susceptibility to Infection in Newborn Infants," *Current Opinion in Infectious Diseases* 26, no. 3 (2013): 248–253, https://doi.org/10.1097/qco.0b013e3283607a58.

24. M. R. Steedman, B. Kampmann, E. Schillings, H. Al Kuwari, and A. Darzi, "Strategies to Boost Maternal Immunization to Achieve Further Gains in Improved Maternal and Newborn Health," *Health Affairs* 35, no. 2 (2016): 309–316, https://doi.org/10.1377/hlthaff.2015.1090.

25. F. M. Munoz and D. J. Jamieson, "Maternal Immunization," *Obstetrics & Gynecology* 133, no. 4 (2019): 739–753, https://doi.org/10.1097/aog.0000000000003161.

26. I. Buka, S. Koranteng, and A. R. O. Vargas, "Trends in Childhood Cancer Incidence: Review of Environmental Linkages," *Pediatric Clinics of North America* 54, no. 1 (2007): 177–203, https://doi.org/10.1016/j.pcl.2006.11.010.

27. S. B. Dixon, K. L. Bjornard, N. M. Alberts, et al., "Factors Influencing Risk-Based Care of the Childhood Cancer Survivor in the 21st Century," *CA: A Cancer Journal for Clinicians* 68, no. 2 (2018): 133–152, https://doi.org/10.3322/caac.21445.

28. M. Kakunje, N. Bharadwaj, K. S. Alex, V. Bharadwaj, and A. Prakash, "COVID-19 Pandemic and Childhood Cancer: Lessons Learnt From a Pediatric Oncology Unit in a Developing Country," *Asian Pacific Journal of Cancer Care* 8, no. 1 (2023): 213–218, https://doi.org/10.31557/apjcc.2023.8.1.213-218.

29. G. K. Swamy and R. Garcia-Putnam, "Maternal Immunization to Benefit the Mother, Fetus, and Infant," *Obstetrics and Gynecology Clinics* 41, no. 4 (2014): 521–534, https://doi.org/10.1016/j.ogc.2014.08.001.

30. F. M. Munoz and S. S. Long, "The Safety of Maternal Influenza Vaccination and Infant Health Outcomes," *Pediatrics* 146, no. 2 (2020): e2020006916, https://doi.org/10.1542/peds.2020-006916.

31. N. Bergin, J. Murtagh, and R. K. Philip, "Maternal Vaccination as an Essential Component of Life-Course Immunization and its Contribution to Preventive Neonatology," *International Journal of Environmental Research and Public Health* 15, no. 5 (2018): 847, https://doi.org/10.3390/ijerph15050847.

32. H. Tashiro and M. K. Brenner, "Immunotherapy Against Cancer-Related Viruses," *Cell Research* 27, no. 1 (2017): 59–73, https://doi.org/10.1038/cr.2016.153.

33. V. Vedham, M. Verma, and S. Mahabir, "Early-life Exposures to Infectious Agents and Later Cancer Development," *Cancer Medicine* 4, no. 12 (2015): 1908–1922, https://doi.org/10.1002/cam4.538.

34. J. S. Laurent, R. Luckett, and S. Feldman, "HPV Vaccination and the Effects on Rates of HPV-Related Cancers," *Current Problems in Cancer* 42, no. 5 (2018): 493–506, https://doi.org/10.1016/j.currproblcancer.2018.06.004.

35. M. C. Nunes, C. L. Cutland, S. Jones, et al., "Efficacy of Maternal Influenza Vaccination Against All-Cause Lower Respiratory Tract Infection Hospitalizations in Young Infants: Results From a Randomized Controlled Trial," *Clinical Infectious Diseases* 65, no. 7 (2017): 1066–1071, https://doi.org/10.1093/cid/cix497.

36. B. Abu-Raya, K. Maertens, K. M. Edwards, et al., "Global Perspectives on Immunization During Pregnancy and Priorities for Future Research and Development: An International Consensus Statement," *Frontiers in Immunology* 11 (2020): 1282, https://doi.org/10.3389/fimmu.2020.01282.

37. J. Boonyaratanakornkit and H. Y. Chu, "Why Should We Advocate Maternal Immunization?," *Pediatric Infectious Disease Journal* 38, no. 6S (2019): S28–S32, https://doi.org/10.1097/inf.0000000000002312.

38. M. L. Giles and A. C. Cheng, "Regulatory Agencies Have a Role to Play in Maintaining Consumer Confidence in Vaccine Safety for Pregnant Women," *Human Vaccines & Immunotherapeutics* 16, no. 10 (2020): 2573–2576, https://doi.org/10.1080/21645515.2020.1718976.

39. W. D. Thompson and D. T. Janerich, "Maternal Age at Birth and Risk of Breast Cancer in Daughters," *Epidemiology* 1, no. 2 (1990): 101–106, https://doi.org/10.1097/00001648-199003000-00004.

40. Z. Liu, Q. Yang, N. Cai, L. Jin, T. Zhang, and X. Chen, "Enigmatic Differences by Sex in Cancer Incidence: Evidence From Childhood Cancers," *American Journal of Epidemiology* 188, no. 6 (2019): 1130–1135, https://doi.org/10.1093/aje/kwz058.

41. D. A. Siegel, J. King, E. Tai, N. Buchanan, U. A. Ajani, and J. Li, "Cancer Incidence Rates and Trends Among Children and Adolescents in the United States, 2001–2009," *Pediatrics* 134, no. 4 (2014): e945–e955, https://doi.org/10.1542/peds.2013-3926.

42. D. A. Schwartz, "An Analysis of 38 Pregnant Women With COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes," *Archives of Pathology & Laboratory Medicine* 144, no. 7 (2020): 799–805, https://doi.org/10.5858/arpa.2020-0901-sa.

43. T. Wainstock, I. Yoles, R. Sergienko, and E. Sheiner, "Prenatal Maternal COVID-19 Vaccination and Pregnancy Outcomes," *Vaccine* 39, no. 41 (2021): 6037–6040, https://doi.org/10.1016/j.vaccine.2021.09.012.

44. C. Montagnoli, S. Ruggeri, G. Cinelli, et al., "Anything New About Paternal Contribution to Reproductive Outcomes? A Review of the Evidence," *World Journal of Men's Health* 39, no. 4 (2021): 626, https://doi.org/10.5534/wjmh.200147.

45. F. Riccardo, A. Réal, C. Voena, R. Chiarle, F. Cavallo, and G. Barutello, "Maternal Immunization: New Perspectives on its Application Against Non-Infectious Related Diseases in Newborns," *Vaccines* 5, no. 3 (2017): 20, https://doi.org/10.3390/vaccines5030020.

46. E. Ø Carlsen, M. C. Magnus, L. Oakley, et al., "Association of COVID-19 Vaccination During Pregnancy With Incidence of SARS-CoV-2 Infection in Infants," *JAMA Internal Medicine* 182, no. 8 (2022): 825–831, https://doi.org/10.1001/jamainternmed.2022.2442.

47. S. S. Coughlin, "A Review of Social Determinants of Prostate Cancer Risk, Stage, and Survival," *Prostate International* 8, no. 2 (2020): 49–54, https://doi.org/10.1016/j.prnil.2019.08.001.

48. K. C. Chu and S. Springfield, "Determinants of Cancer Health Disparities: Barriers to Cancer Prevention, Screening, Diagnosis and Treatment," *Expert Opinion on Medical Diagnostics* 2, no. 5 (2008): 467–473, https://doi.org/10.1517/17530059.2.5.467.

49. A. N. Faucette, B. L. Unger, B. Gonik, and K. Chen, "Maternal Vaccination: Moving the Science Forward," *Human Reproduction Update* 21, no. 1 (2015): 119–135, https://doi.org/10.1093/humupd/dmu041.

50. D. B. Fell, E. Azziz-Baumgartner, M. G. Baker, et al., "Influenza Epidemiology and Immunization During Pregnancy: Final Report of a World Health Organization Working Group," *Vaccine* 35, no. 43 (2017): 5738–5750, https://doi.org/10.1016/j.vaccine.2017.08.037.