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Disparities in Infant Mortality Due to Congenital Anomalies on Guam

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Abstract

*In the 1970's and 1980's, there were large inter-village disparities in infant mortality due to congenital anomalies on Guam. A village-level analysis was conducted to determine if these disparities can be explained by behavioral (ie, median age of village females, village fertility ratio), structural (ie, population density, persons per household, single mother households per village, married females per village), and environmental (ie, living in a village where Agent Orange (AO) spraying was conducted) factors. Village-level data for live births and infant mortality due to congenital anomalies (1970-1989) was collected from Guam's Office of Vital Statistics. Data on median age of village females, village fertility ratio, population density, persons per household, single mother households, and married females were obtained from the 1980 US Census. Estimates of village-level AO use were provided through personal communications, and villages were dichotomized into AO and non-AO spray areas. Village location was classified by usual residence of the mother. Linear regression was used to determine associations between infant mortality due to congenital anomalies and the behavioral, structural, and environmental factors. The association between AO spray area and infant mortality due to congenital anomalies was statistically significant under univariable (*B *[95%CI] = 1.88 [0.64,3.11],* P = .005) and multivariable conditions (*B *[95%CI] = 2.02 [0.08,3.96], P = .042). These results suggest that infants born to mothers whose usual residence was in an AO spray area on Guam are at an increased risk of mortality due to congenital anomalies. Further studies using individual-level data are needed to validate these results.*

Keywords

Agent Orange, Guam, Infant, Mortality

Introduction

Guam is a United States (US) territory located in the Western Pacific Ocean. It is the southernmost island of the Mariana Archipelago and is the largest and most populous island in the Micronesian region.[1] In the 1970's and 1980's, Guam experienced large disparities in infant mortality due to congenital anomalies that have gone unexplained. While some villages reported no infant deaths due to congenital anomalies, others reported cause-specific infant death rates as high as 5.62 deaths per 1,000 live births, a figure that was two times greater than the overall cause-specific death rate on Guam (2.43 deaths per 1,000 live births) and in the US (2.5 deaths per 1,000 live births).[2]

There are several possible behavioral, structural, and environmental explanations for these differences. At the behavioral level, mothers in high-risk villages may give birth at older ages compared to mothers in other villages. Several studies have identified advanced maternal age as a significant risk factor for genetic anomalies and stillbirth.[3,4] In a review of 142 studies, advanced maternal age was associated with a 2.31-5.46 greater odds of stillbirth, and the odds of stillbirth due to congenital anomalies was found to be 7.5 (OR [95%CI] = 7.50 [3.2, 17.4]).[5] Mothers in high risk villages may also have more children than mothers in low risk villages. Statistically significant associations between high fertility rates and child mortality were found in a study of 47 low and middle income countries, although the authors were unable to explain the mechanism that drives this relationship.[6]

Structurally, community and family dynamics may explain differences in infant mortality due to congenital anomalies. Urban environments have been associated with significant increases in congenital anomalies and infant mortality in Asia and Europe.[7-10] For example, congenital anomalies decreased significantly in rural areas of Henan Province in China between 1997 and 2011 ($P < .001$) but increased significantly in urban locations ($P = .003$).[9] Family dynamics may encompass both the number of individuals living in a household or single parent households. The Particulate Matter and Perinatal Events Research (PAMPER) study discovered that both infant mortality and family size decreased between 1961 and 1992,[11] and in a separate study of 28,647 children conducted in Nigeria, small family size was associated with decreased under-5 mortality.[12] Moreover, a study of approximately 49,000 children in Cameroon, Nigeria, and the Democratic Republic of the Congo determined that under-5 mortality was significantly, or marginally significantly, higher in children of non-widowed single mothers.[13]

Certain environmental exposures, such as herbicides, may also be associated with infant death due to congenital anomalies. In 2005 and again in 2013, the Department of Veterans Affairs (VA) concluded that herbicides, particularly Agent Orange (AO), were used on Guam from 1968 to 1970.[14,15] AO is a mixture of two herbicides: 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D),[16] and has been linked to numerous health effects, primarily caused by contamination of 2,5,4-T with 2,3,7,8-tetrachlorodibenzodioxin (TCDD). TCDD has been classified as carcinogenic to humans by the International Agency for Research on Cancer and as a probable human carcinogen by the US Environmental Protection Agency (EPA).[17,18] There is also evidence suggesting that AO exposure is associated with ischemic heart disease, Parkinson's disease, and respiratory cancers.[19]

Infant and fetal AO exposure can occur through paternal and maternal mechanisms, with recent evidence showing breast milk as an important AO vector.[20] The potential effects of AO on offspring have been known since 1969 when offspring of mice exposed to contaminated 2,4,5-T were shown to be at an increased risk of developing congenital anomalies.[16] A meta-analysis on human AO exposure concluded that AO significantly increased the risk of birth defects, although significant between-study

heterogeneity occurred and the authors expressed concern about publication bias.[21] Moreover, children of fathers who served in southeast Asia during the Vietnam War and participated in Operation Ranch Hand, the US Department of Defense's defoliation program during the war, had significantly greater risk of infant death compared to children of fathers who served in southeast Asia but did not participate in the operation.[22]

The reason for the disparities in infant mortality due to congenital anomalies on Guam are currently unknown. The purpose of this study is to determine if behavioral, structural, or environmental factors are associated with village-level infant mortality due to congenital anomalies.

Methods

Total births by village and infant mortality due to congenital anomalies were made available from the Office of Vital Statistics in the Guam Department of Public Health and Public Services for each year from 1970-1989. Infant mortality due to congenital anomalies was determined using ICD-8 and ICD-9 codes 740-759, and the cause specific mortality rate was defined as deaths per 1,000 live births. Village assignment for each birth and death was based on the usual residence of the mother. All villages on Guam were included in the analysis (N = 19); however, births and deaths from mothers whose usual residence was a military base or unknown were excluded because of the inability to assess potential behavioral, structural, or environmental exposure levels and their relatively brief exposure to the Guam environment.

Village-level estimates for behavioral and structural exposures were obtained from the 1980 US Census. Census data was included due to the standardized methodology and completeness of data collection. The 1980 Census was used because data collection occurred near the mid-point of the study period. Median age of village females (in years) and the village fertility ratio (ie, the number of children under 5 years old per 1,000 women 15 to 49 years old) were used to assess behavioral exposures. Population density (persons per square kilometer) was used to control for difference in community dynamics. Persons per household, single mother households (per 1,000 families), and married females (per 1,000 females 15 years old and over) were used to control for differences in family dynamics.

Although the VA has concluded that herbicides and AO were used on Guam, exact levels of AO used were unavailable, and the EPA concluded that there are no historical documents related to hazardous chemical use or disposal on Guam.[23] However, a US Air Force Veteran who conducted ground-level AO spraying for vegetation control was able to provide village-level spray estimates based on the recollection of this spray routine (Foster L., Personal Communication). This information was used to dichotomize villages into AO and non-AO spray areas. The Veteran has provided documentation substantiating his claims that he conducted AO spraying on Guam. These include a notarized statement describing the Veteran's use of AO on Guam, a notarized photo identifying AO spray areas from a second Veteran who personally witnessed our Veteran spraying AO, medical records demonstrating that the Veteran has suffered from physical reactions consistent with AO exposure, including severe acne consisting of skin eruptions and scarring,[24] images of the Veteran being sworn into active duty with the Air Force, and photos of polydactyly occurring in the Veteran's granddaughter. Additionally, his claims have been reported and confirmed by The Japan Times and the Daily Beast.[25,26] All documents made available to the authors regarding the Veteran's AO claims have been turned over to the journal editors.

All variables included in the analysis were examined for symmetry and skewness prior to analysis. No transformations were needed. Villages were classified based on whether the village infant mortality due to congenital anomalies rate was above (high risk) or below (low risk) the overall rate for the island. Chi-square analysis, Fisher's exact test, and independent sample t-tests were used to identify significant differences in the included factors between high and low risk villages. Univariable linear regression models were created to determine unconditional associations between infant mortality due to congenital anomalies and the selected factors. AO spray area was dummy coded and non-AO spray areas were used as the reference group. The remaining independent variables and village infant mortality due to congenital anomalies were treated as continuous variables. R^2 values were used to estimate the percent variance in infant death due to congenital anomalies explained. A multivariable linear regression model was created to determine conditional

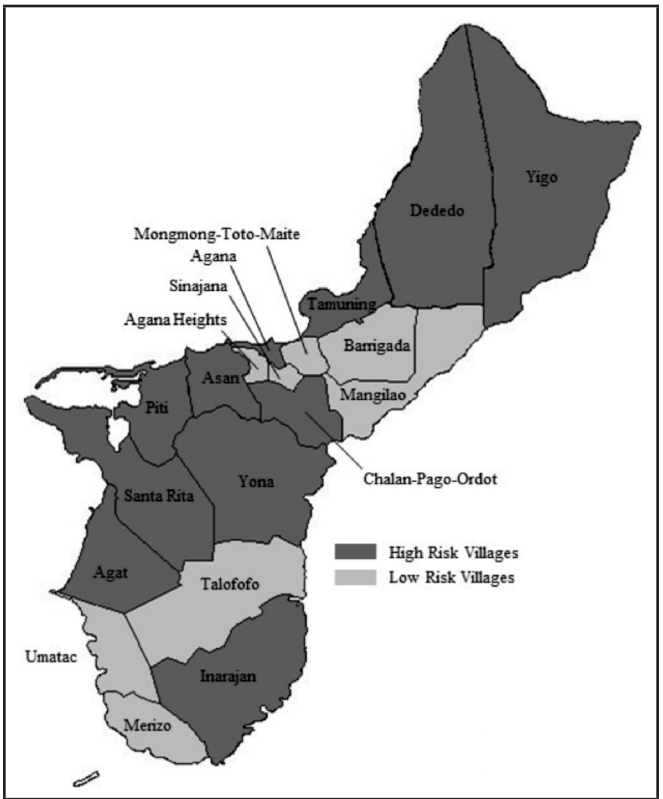

Figure 1. Villages of Guam Above (High Risk) and Below (Low Risk) Guam's Overall Rate of Infant Mortality due to Congenital Anomalies

significant associations. Multicollinearity was assessed using variance inflation factors (VIF). Variables with a VIF greater than 10 were examined and removed if significantly correlated with other variables in the model. The analysis was conducted using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY, USA), and statistical significant was set at 0.05 a priori.

Results

Eleven villages on Guam were classified as high risk villages and eight were classified as low risk villages (Figure 1). From 1970-1989, there were 121 infant deaths due to congenital anomalies among 49,841 live births on Guam, resulting in a cause-specific death rate of 2.43 per 1,000 live births (Table 1). Congenital anomalies included congenital heart disease, anencephaly, and diaphragmatic hernia. Within high risk villages, the cause-specific death rate was 2.96 per 1,000 live births while the rate was 1.31 per 1,000 live births among low risk villages. The difference between these values was statistically significant ($\chi^2(1) = 11.628$, $P < .001$).

Table 1. Infant Mortality due to Congenital Anomalies (1970-1989) by Village*

Village	Infant Deaths	Live Births	Infant Mortality Rate (/1,000 Live Births)
High Risk			
Asan	5	889	5.62
Piti	5	948	5.27
Chalan-Pago-Ordot	8	1,905	4.20
Agat	10	2,999	3.33
Yona	8	2,412	3.32
Inarajan	4	1,308	3.06
Agana	3	1,106	2.71
Santa Rita	4	1,516	2.64
Dededo	29	11,257	2.58
Tamuning	17	6,635	2.56
Yigo	7	2,797	2.50
Sub-Total	100	33,772	2.96
Low Risk			
Merizo	2	1,022	1.96
Barrigada	6	3,620	1.66
Mongmong-Toto-Maite	5	3,036	1.65
Agana Heights	2	1,413	1.42
Mangilao	4	3,278	1.22
Sinajana	2	1,926	1.04
Talofofo	0	1,271	0.0
Umatac	0	503	0.0
Sub-Total	21	16,069	1.31
Total	121	49,841	2.43

*Village of mother's usual residence

Overall mean median age of village females was 21.7 years (SD = 2.27) and the mean fertility ratio was 468.9 children under 5 years old per 1,000 women 15 to 49 years old (Table 2). There were approximately 367 persons per square kilometer and 4.24 persons per household. There were 90.8 single mother households per 1,000 families, and there were 384.0 females married per 1,000 females 15 years old and over. Twelve villages were classified as AO spray areas. There was a statistically significant association between village type and AO spray area ($P = .006$). No other statistically significant differences based on village type were detected (P's = .065-.921).

Table 2. Descriptive Statistics of Independent Variables[a]

Variable	Overall	High Risk Villages[b]	Low Risk Villages[b]	T[e]	P[f]
Median Age of Village Females[c]	21.7 (2.27)	22.1 (2.32)	21.0 (2.18)	1.05	.307
Fertility Ratioc	468.9 (81.0)	470.4 (101.7)	466.9 (45.7)	0.10	.921
Population Densityc	366.5 (401.5)	246.7 (245.7)	531.3 (524.2)	1.43	.187
Persons per Household[c]	4.24 (0.67)	4.11 (0.69)	4.42 (0.64)	1.01	.326
Single Mother Households[c]	90.8 (31.6)	81.9 (29.8)	103.0 (31.7)	1.49	.155
Females Married[c]	384.0 (51.5)	402.5 (50.3)	358.6 (43.9)	1.98	.065
AO Spray Villages[d]	12 (63.2)	10 (90.9)	2 (25.0)		.006

[a]Mean (SD); [b]Data from the Office of Vital Statistics in the Guam Department of Public Health and Public Services; [c]Data from the 1980 US Census; [d]Fisher's exact test was used, no t-statistic was produced; [e]the T statistic is calculated by dividing the difference between groups by the standard error of the total sample; [f]P < .05 is considered statistically significant. AO, agent orange.

Univariable linear regression determined that the association between AO spray area and infant mortality due to congenital anomalies was statistically significant (B [95%CI] = 1.88 [0.64, 3.11], $P = .005$) (Table 3). AO spray area explained approximately 38% of the variance ($R^2 = 0.38$). There were no other statistically significant associations with infant mortality due to congenital anomalies (P's = .111-.400).

In the multivariable linear regression model, median age of village females, persons per household, and married females exhibited high multicollinearity (VIF's = 12.17-25.83). Therefore, three multivariable models were created, each using only one of the correlated variables plus three additional covariates (fertility ratio, population density, and single mother households). Under multivariable conditions that included median age of village females (Model 1), the association between AO spray area and infant mortality due to congenital anomalies was statistically significant (B [95% CI] = 2.02 [0.08, 3.96], $P = .042$), and the model explained approximately 51% of the variance ($R^2 = 0.51$) (Table 4). No other covariates were statistically significant (P's = .244-.687). Similar statistically significant coefficients

for AO spray area were produced when median age of village females was replaced by persons per household (Model 2) (*B* [95% CI] = 1.71 [0.04, 3.39], *P* = .046) and married females (Model 3) (*B* [95% CI] = 1.82 [0.08, 3.55], *P* = .042).

Discussion

Infants of mothers whose usual residence was in AO spray areas had an increased risk of mortality due to congenital anomalies compared to infants of mothers whose usual residence was in non-AO spray areas. AO spray area was the only statistically significant predictor of infant mortality due to congenital anomalies under univariable and multivariable conditions. This increased risk is unlikely to be due to overall greater rates of infant mortality due to congenital anomalies on Guam. Indeed, the mean US infant mortality rate due to congenital anomalies between 1970 and 1989 was 2.5 deaths per 1,000 live births, slightly greater than that of Guam found here.[2]

Significant associations between AO and infant mortality are consistent with previously published literature. In a meta-analysis of 9 peer-reviewed and 13 unpublished studies, parental exposure to AO resulted in a 95% increased risk of birth defects (RR 95% CI) = 1.95 (1.59, 2.39).[21] The risk of birth defects was dose dependent, with studies in Vietnamese populations producing greater relative risk estimates (RR (95% CI) = 3.00 (2.19, 4.12) than studies in non-Vietnamese populations (RR (95% CI) = 1.29 (1.04, 1.59). A later meta-analysis of 4 peer-reviewed and 3 unpublished studies determined that the pooled relative risk for spina bifida, a birth

Table 3. Associations between Village-Level Variables and Infant Death due to Congenital Anomalies, Univariable Linear Regression

Variable	B	95% CI	T[a]	*P*[b]	R^2
AO Spray Area	1.88	0.64, 3.11	3.21	.005	0.38
Median Age of Village Females	0.20	-0.13, 0.53	1.30	.213	0.09
Fertility Ratio	-0.004	-0.01, 0.01	0.86	.400	0.04
Population Density	-0.001	-0.003, 0.001	1.14	.270	0.02
Persons per Household	-0.73	-1.83, 0.37	1.41	.178	0.05
Single Mother Households	-0.01	-0.04, 0.01	1.03	.317	0.06
Married Females	0.01	-0.003, 0.03	1.68	.111	0.14

[a]the T statistic is calculated by dividing B by the standard error of B; [b]P < .05 is considered statistically significant. AO, agent orange; CI, confidence interval.

Table 4. Associations between Village-Level Variables and Infant Death due to Congenital Anomalies, Multivariable Linear Regression

Variable	B	95% CI	T[a]	*P*[b]
Model 1[c]				
AO Spray Area	2.02	0.08, 3.96	2.25	.042
Median Age of Village Females	-0.16	-0.82, 0.50	0.53	.607
Fertility Ratio	-0.008	-0.02, 0.01	1.22	.244
Population Density	-0.001	-0.003, 0.002	0.78	.450
Single Mother Households	-0.005	-0.03, 0.02	0.41	.687
Model 2[d]				
AO Spray Area	1.71	0.04, 3.39	2.21	.046
Persons per Household	0.48	-2.08, 2.17	0.05	.962
Fertility Ratio	-0.005	-0.02, 0.01	0.82	.427
Population Density	-0.001	-0.004, 0.001	1.10	.290
Single Mother Households	-0.003	-0.04, 0.03	0.19	.852
Model 3[e]				
AO Spray Area	1.82	0.08, 3.55	2.26	.042
Married Females	-0.003	-0.03, 0.02	0.26	.798
Fertility Ratio	-0.01	-0.02, 0.004	1.26	.230
Population Density	-0.001	-0.003, 0.001	1.25	.232
Single Mother Households	-0.01	-0.05, 0.03	0.33	.745

[a]the T statistic is calculated by dividing B by the standard error of B; [b]P < .05 is considered statistically significant; [c]R2 = 0.51; [d]R2 = 0.50 ; [e]R2 = 0.50.
AO, agent orange; CI, confidence interval

defect resulting in the incomplete closer of the spinal column around the spinal cord, after paternal AO exposure was 2.02 (95% CI = 1.48, 2.74).[27] Moreover, paternal AO exposure has been previously linked with increased risk of infant death.[22]

There are two possible explanations for why all other included independent variables were non-significant. First, there may be a high degree of homogeneity within Guamanian communities and in individual behavior patterns. Indeed, at only 571 square kilometers, Guam is the smallest US territory,[28] and in 1980, the island's population was only 106,000 individuals.[29] Second, non-significant associations may have occurred due to inadequate sample size. Because the analysis was conducted at the village-level, the maximum sample size available was 19, regardless of how many births and infant deaths had actually occurred. This value may have been insufficient to detect true associations between non-significant variables and infant mortality due to congenital anomalies.

There are several limitations to this study. Exact levels of AO spraying that occurred on Guam during the Vietnam War could not be specified and official records likely do not exist.[23] The study relied primarily on the recollection of one individual who claimed to be in charge of AO spraying. Although his claims have been verified by others, caution is required because he may harbor significant biases due to suffering from conditions associated with AO exposure. Furthermore, confirmatory laboratory testing to determine whether any individual included in the study was exposed to AO could not be performed, although environmental AO may pose a threat for years after initial spraying due to its long half-life, that is typically 11-15 years in humans and has been observed to be as long as 20 years.[30] In the environment, AO's half-life is heavily dependent on soil type and depth of penetration. When exposed to sun, primarily on leaf and soil surfaces, TCDD will break down in 1 to 3 years.[31] When under the soil surface or deep within the sediment of rivers and other bodies of water, TCDD's half-life can be more than 100 years.

Village-level data on some potential confounders were identified, although the list is not exhaustive. Data on race, ethnicity, socioeconomic factors, infectious disease rates, maternal nutritional status, and other environmental factors were not included. It is possible that survival could be a function of socioeconomic status because of restricted healthcare access. Healthcare access for many Pacific Islanders has often been limited, with many needing to travel to Hawai'i or the US mainland to see a specialist. Only recently has healthcare access been expanded in the Pacific Islands, primarily through telemedicine programs.[32] Additionally, the reliance on vital statistics data may diminish study validity because such databases may be incomplete and data quality may be poor.[33]

The study presented here is the first to identify associations between AO and infant mortality in civilian populations outside of Southeast Asia, but it is important to stress that the ecological design of the study makes causal inferences of the study results impossible. The results, however, do propose intriguing hypotheses regarding the impact of AO on Guam, and there are several follow-up studies that are needed to confirm the association between AO and infant mortality due to congenital anomalies. Case-control and retrospective cohort studies need to be conducted to determine if the association remains when individual data is used. These studies should use multiple control groups, including populations from non-AO spray areas on Guam, other Pacific islands where AO was never used or stored, and unexposed areas of the contiguous US. Because of AO's potentially long half-life, environmental studies are also required to determine if AO has persisted in the Guamanian soil, and if present, studies of the current population on Guam area needed to determine if AO continues to be a public health threat.

In conclusion, the results suggest that infants born to mothers who resided in AO spray areas were at an increased risk of infant mortality due to congenital anomalies. This is the first study to examine the link between AO and infant mortality on Guam. Further studies using individual-level data are required to validate the claims of the Veteran and confirm a link between AO and infant mortality on Guam. Additional studies should also determine if excess risk of infant mortality on Guam exists decades after AO spraying ceased.

Conflict of Interest

None of the authors identify a conflict of interest.

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