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Risk Factors for Pneumonia-Associated Infant Death in the United States, 2007-2010

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Abstract

Risk Factors for Pneumonia-Associated Infant Death in the United States, 2007-2010
By: Sharada Ramakrishnan

PURPOSE: The objective of this study was to determine maternal and infant risk factors associated with pneumonia-associated infant death in the United States.

METHODS: Using the United States Period Linked Birth/Infant Death data for 2007-2010, a retrospective case-control study was conducted to determine infant and maternal risk factors for pneumonia-associated infant death among singleton infants born in the United States. A pneumonia-associated death was defined by the presence of an International Classification of Diseases, Tenth Revision (ICD-10) code for pneumonia (J12 – J18). Infants who survived their first year were randomly selected as controls to obtain a 1 to 4 ratio of cases to controls. Risk factors for pneumonia-associated infant death were determined using multivariable logistic regression modeling.

RESULTS: The infant mortality rate for pneumonia-associated infant death during 2007-2010 in the United States was 10.7. Male sex was associated with higher odds of pneumonia-associated death (OR 1.45, 95% CI 1.28-1.64) compared to females, infants with a 5-minute Apgar score <7 had higher odds (OR 7.41, 95% CI 5.53-10.01) of pneumonia-associated death compared to infants with a score ≥7. The American Indian/Alaska Native race group had the highest odds of pneumonia-associated death (OR 2.23, 95% CI 1.48-3.31) compared to the White race group. Among both low and normal birth weight infants, those born first in live birth order had lower odds of pneumonia-associated death compared to those born second in live birth order. Among low birth weight infants, the maternal age category of 20-24 years had a higher odds of pneumonia-associated death, whereas for normal birth weight, those with maternal age ≤19 had a higher odds.

DISCUSSION: Pneumonia is one of the top ten leading causes of death in the United States. The findings in this study are relevant for reducing the impact of pneumonia-associated death in the United States. Health care providers and mothers will be able identify methods for prevention of pneumonia during prenatal care, and awareness of risk factors will lead to an overall decrease in the rate of pneumonia-associated death.

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1. Introduction

1.1. Disease Definition

Pneumonia is an infection of the lungs. Using a system of host defenses, the lung removes and prevents microorganisms from gaining access to it. If the process is broken, however, organisms can intrude. The effects of the resulting microorganism multiplication and host response can result in the clinical condition pneumonia. Pneumonia is classified based on the origin of infection. Each classification may imply a different etiology, treatment, and prognosis. "Community-acquired pneumonia" (CAP) refers to infection that has appeared in a non-hospitalized individual with no risk factors for multi-drug-resistant pathogens. "Hospital acquired pneumonia" (HAP) or "nosocomial pneumonia" refers to cases for which there is no evidence that an infection was present at the time of hospital admission (IEPH 2014).

Community-acquired pneumonia in the United States affects more than four million adults per year, accounting for more than one million hospital admissions per year (IEPH 2014). This condition is also prevalent in non-industrialized and less developed countries (IEPH 2014). In adults, the incidence ranges from 1.6 to 11 per 1000 adults per year worldwide (IEPH 2014). Incidence is higher among the elderly and among men of all ages. Pneumonia in the United States is among the top ten leading causes of death, and worldwide, it is the leading cause of mortality in children under the age of five (WHO 2013, IEPH 2014).

1.2. Symptoms and Treatment/Management

Symptoms of pneumonia include cough, sputum production, pleuritic chest pain, and dyspnea. Diagnosis of the disease requires detection of the presence of an infiltrate on a chest x-ray. Presence of this infiltrate confirms the diagnosis, but it is still difficult to determine a specific etiologic agent. There are a small number of key pathogens that cause most cases, the most predominant of which is *Streptococcus pneumonia*, which accounts for about two-thirds of bacteremic pneumonia. Additionally, concurrent infection by multiple microorganisms may lead to CAP (IEPH 2014).

Management of CAP involves determining the most appropriate care setting: hospital ward, intensive care unit, or outpatient clinic. The decision to hospitalize a patient is based on the stability of the condition, the presence of other medical problems, and the risk of other complications or death. In order to evaluate these options, a prediction score called the "pneumonia severity index" (PSI) is used (Eerden 2004, IEPH 2014). This index places patients into one of five risk categories, where higher scores mean a higher risk of death. Patients in classes I and II can be treated as outpatients since they have a 30-day mortality risk of lower than 1%. Class III patients have a risk of death between 0.9% and 2.9%. These patients should be kept in the hospital for a short period for observation. The risk of death for patients in classes IV and V is between 8.9% and 29.2%. These patients should be hospitalized. The risk of worsening is highest during the first 24 hours after presentation and decreases thereafter (IEPH 2014).

Another score that is sometimes used to determine appropriate patient care is called the "CURB 65" score. This addresses five variables which are each assigned one point: *C*onfusion, *U*rea greater than 7mmol/L, *R*espiratory rate greater than 30 per minute, *B*lood pressure low with systolic < 90mm Hg or diastolic ≤ 60mm Hg, and age over *65*. Those with a CURB-65 score of 1 have a risk of death of 1.5% and are treated as outpatients. Those with scores of 2 or higher are considered for hospitalization, and those with scores of 3 or higher are admitted to an Intensive Care Unit (ICU) (IEPH 2014).

There are a few options for diagnostic testing, including blood cultures and sputum samples, but such tests are only conducted if there is a suspicion of a specific pathogen or if such a diagnosis might change the treatment management decisions. Blood cultures have a sensitivity of only 5-14%; however, they are still conducted in cases of severe CAP, ICU patients, and cases of immunosuppression. There are urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophilia*. This test is simple and able to detect, with reasonable accuracy, a specific pathogen (IEPH 2014).

1.3. Immunization and Treatment

Pneumonia vaccines are the current leading preventive measure for CAP. For those who are 65 years of age and older and for those with compromised immune systems, the pneumococcal polysaccharide vaccine is recommended. Those who are

at least 50 years of age, have contact with high-risk persons, or are health-care workers are recommended the pneumococci and influenza vaccine.

For inpatient child cases, children aged 4 months to 4 years are given amoxicillin, and those aged 5 to 15 years are given amoxicillin and macrolides. For outpatient cases, those with *Streptococcus pneumoniae* who are 4 months to 4 years of age are given Penicillin G or Amoxicillin, and those with *Streptococcus pneumoniae* who are 5 to 15 years of age are given Penicillin G or Amoxicillin Cefuroxime. Outpatients with *Haemophilus influenzae, Staphylococcus aureus,* or a suspected pen-resistant *Streptococcus pneumoniae* who are between 4 months and 15 years of age are given Cefuroxime, and outpatients with *Mycoplasma pneumoniae* or a suspected *Chlamydophilia* in the same age group are given Penicillin G plus macrolide (IEPH 2014).

1.4.Causes and Known Risk Factors

The most common causes of CAP in outpatients are *Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilius influenzae, Chlamydophilia pneumoniae,* and respiratory viruses (Wundernlk 2007). In non-ICU patients, the most common causes include all of the above and also *Legionella* species (Wundernlk 2007). Among ICU patients, the most common causative factors are: *Streptococcus pneumoniae, Haemophilius influenzae, Legionella* species, Gram-negative bacilli, and *Staphylococcus aureus* (Wundernlk 2007).

Some risk factors for CAP are related to specific pathogens. Alcoholism, for example, is a risk factor for *Streptococcus pneumoniae,* oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* species, and *Myobacterium tuberculosis.* Chronic obstructive pulmonary disease and smoking are risk factors for *Haemophilius influenzae, Pseudomonas aerginosa, Legionella* species, *Streptococcus pneumoniae, Moraxella cararrhalis,* and *Chlamydophila pneumoniae.* Additionally, a stay in a hotel or cruise ship within the previous two weeks is a risk factor for *Legionella* species. Some other risk factors include active influenza in the community, structural lung disease, injection drug use, exposure to bird droppings, endobronchial obstruction, and early HIV infection (IEPH 2014).

The objective of this study is to determine maternal and infant risk factors associated with infant deaths associated with pneumonia. The findings in this study may be used by health care providers and mothers to identify methods for prevention of pneumonia during prenatal care.

2. Methods

2.1. Epidemiological Methods and Analyses

The United States Linked Birth/Infant Death data for 2007-2010 were used for this analysis. This is a public use data set provided by the National Center for Health Statistics (NCHS), a division within the Centers for Disease Control and Prevention (CDC) and the United States Department of Health and Human Services (HHS). The United States Linked Birth/Infant Death data provides information on various

maternal and infant characteristics for infants (children less than one year of age) who died in the given year (NCHS 2010, 2011, 2012, 2013). The infant death certificate is linked to the corresponding birth certificate allowing for the analysis of factors that may be associated with death. Death certificates which could not be matched to birth certificates were excluded from this analysis. To account for this missing data, the number of pneumonia-associated deaths was weighted. The weight was computed by adding the number of linked and unlinked infant deaths and then dividing by the number of linked infant deaths. In 2007, 1.6% of infant death records were unlinked. 1.3% were unlinked in 2008, 1.4% in 2009, and 1.2% in 2010.

Pneumonia-associated deaths were defined as records that listed an *International Classification of Diseases, Tenth Revision* (ICD-10) code for pneumonia (J12-J18) anywhere on the death record (Table 1). A retrospective case-control study was conducted to identify potential maternal and infant risk factors for infant deaths associated with pneumonia. Cases were defined as pneumonia-associated deaths among singleton infants, and controls were defined as singleton infants who survived the first year of life and were randomly selected from the United States Linked Birth/Infant Death dataset to obtain a 1:4 ratio of cases to controls.

Infant mortality rates (IMRs), expressed as the weighted number of pneumonia-associated deaths per 100,000 live births were calculated for sex, birth weight, maternal race, 5-minute Apgar score, maternal marital status, and live birth order. Rate ratios (RRs) and 95% confidence intervals (CIs) were computed using Poisson regression for the comparison of rates between groups (Kutner 2005).

Odds ratios (ORs) and corresponding 95% CIs were calculated by cases and controls for univariate variables and for those included in the model. An OR greater than 1 means that the risk factor is associated with a higher odds of pneumonia-associated death, while an OR less than 1 indicates that the risk factor is associated with a lower odds of pneumonia-associated death. If the OR is equal to 1, then there is no evidence of an effect of the risk factor on the odds of pneumonia-associated death. These values were calculated using SAS version 9.3.

2.2. Maternal and Infant Characteristics and Model Selection

The maternal and infant characteristics analyzed were chosen based on previous literature as well as data availability (Singleton 2009). Two versions of the birth certificate are currently in use. Some characteristics were recorded differently among the 1989 and 2003 revisions of the U.S. Standard Certificate of Live Birth and were thus not comparable. From 2007-2010, 64.9% of pneumonia-associated deaths used the 2003 revision. Thus, some variables, such as tobacco consumption could not be analyzed without excluding a substantial number of infants.

The characteristics analyzed include: maternal race [White, Black, Asian/Pacific Islander (A/PI), and American Indian/Alaska Native (AI/AN)], infant birth weight [low birth weight (<2500g) and normal birth weight ($\geq$ 2500g)], gestational age (<37 weeks and $\geq$37 weeks), sex, maternal Hispanic origin, live birth order (first, second, and third or more), 5-minute Apgar score (<7 and $\geq$7), maternal age at delivery ($\leq$19, 20-24, 25-29, and $\geq$30), maternal marital status, and maternal

diabetes. Since birth weight and gestational age are correlated, both variables could not be considered in the same model. Birth weight was selected over gestational age because of more reliable reporting (Singleton 2009).

A Pearson chi-squared test was initially conducted to test for univariate significance, defined by a p-value < 0.1. All significant predictors in the univariate analysis and all possible two-way interaction terms were entered into an initial multivariable logistic regression model. Hierarchical backward elimination was used and a p-value < 0.05 indicated statistical significance for inclusion in the model. At each step, the full model was compared to every possible reduced model with one predictor removed. The difference in the -2 log-likelihood values for each model was used to compute a p-value using the likelihood ratio test. The least significant predictor was removed, and the reduced model was selected as the new full model. The process was repeated until all remaining predictors were significant.

3. Results

3.1. Infant Mortality Rates

There were 1734 weighted pneumonia-associated infant deaths in 2007-2010 among singleton infants in the United States. The overall IMR was 10.7 per 100,000 live births. The IMR for males was higher compared to females, and the IMR for LBW infants was higher compared to NBW infants. The IMR for the AI/AN race category was higher than each other race category. For infants with a 5-minute Apgar score <7 the IMR was more than ten times the IMR for infants with an Apgar score

≥7. The IMR for the maternal age group of ≤19 was highest compared to all other age groups. Infants with unmarried mothers had an IMR of more than twice that of infants with married mothers. Infants who were born third or later in live birth order had a higher IMR than infants who were born first or second in live birth order (Table 3).

3.2. Risk Factors

The final model contained the following variables: maternal marital status, sex of infant, 5-minute Apgar score of infant, maternal age at delivery, maternal race, infant live birth order, infant birth weight, the interaction between infant birth weight and infant live birth order, and the interaction between infant birth weight and maternal age at delivery.

Univariate significance included infant Apgar score, where the odds of pneumonia-associated death for infants with a score <7 were 13.47 (95% CI 10.42-17.40) times the odds for infants with a score ≥7. Infants born first in live birth order had lower odds of pneumonia-associated death compared to infants born second, and the odds for those born third or later in live birth order were 1.5 times the odds of infants born second in live birth order. Low birth weight infants had higher odds of pneumonia-associated death compared to normal birth weight infants (Table 2).

Based on the multivariate logistic regression analysis, the odds of pneumonia-associated death for males were 1.45 (95% CI 1.28-1.64) times the odds for females (Table 4). The odds of pneumonia-associated death for infants with an Apgar score <7 were 7.41 times higher compared to those with an Apgar score ≥7. The odds of

pneumonia-associated death for infants born to unmarried mothers were 0.71 times the odds for infants born to married mothers, and the AI/AN race category had higher odds of death compared to the White race category [OR 2.23 (95% CI 1.48-3.31), Table 4].

Among low birth weight infants, the odds for infants born third or later in live birth order were the highest. Among low birth weight infants, odds of pneumonia-associated death were higher where maternal age was 20-24 (1.85, 95% CI 1.27-2.65) compared to maternal age of 25-29. The odds ratio for low birth weight infants with maternal age ≤19 was similar (Table 4).

Among normal birth weight infants, odds of pneumonia-associated death were again higher for those born third or later in live birth order compared to those born second in live birth order. For normal birth infants, those with maternal age ≤19 had 2.47 (95% CI 1.93-3.16) times the odds of death compared to normal birth weight infants with a maternal age of 25-29, whereas the odds for normal birth weight infants with maternal age of 20-24 years were 1.58 (95% CI 1.31-1.89) times the odds for those with maternal age 25-29 years (Table 4).

4. Discussion

Pneumonia kills more children worldwide than any other illness including AIDS, malaria, and measles combined (Wardlaw 2006). The findings in this study are relevant for reducing the impact of pneumonia-associated deaths in the United States.

Approximately 1.1 million children under the age of five die from pneumonia around the world each year (WHO 2013). Since most pneumonia-associated deaths occur among children, the findings of this study may be used to prevent future infant mortality by addressing the identified maternal and infant risk factors for pneumonia-associated infant deaths (Mulholland 2006). Measures to prevent low birth weight, for example, would be effective since the odds of pneumonia-associated deaths for low birth weight infants were consistently higher than the odds for normal birth weight infants. Hospitals and other health care facilities are becoming more equipped to take care of low birth weight infants, and challenges associated with low birth weight babies may decrease over time.

Limitations of this study included the incongruences between the 1989 and 2003 revisions of the U.S. Standard Certificate of Live Birth. Because some information, such as tobacco consumption, was collected differently on the two versions, not all variables were comparable and could not be analyzed for all death records. Additionally, only singleton infants were considered so multiple births with one or more cases of pneumonia-associated deaths were not included in the analyses. The race groups are self-reported and particular groups such as AI/AN and A/PI are often underrepresented. Hospital workers are expected to use the ICD-10 codes to record diseases on the death certificate; however, there may be errors due to misdiagnosis or miscoding.

Health care providers and expecting mothers should be aware of pneumonia-associated infant mortality risk factors. Mothers ≥30 years of age with LBW infants had the greatest odds of pneumonia-associated infant deaths. Future studies looking at causes for low birth weight may be useful for the prevention of such infant deaths. Since infants

of AI/AN mothers have the highest odds of pneumonia-associated deaths among all race groups; AI/AN mothers and their health care providers should be aware of this risk. Infants with unmarried mothers have a lower odds compared to infants with married mothers. A future study might consider a confounder such as maternal education in order to further assess the risk presented to married mothers. Mothers who have given birth previously should be aware of the increased odds for infants born third or later in live birth order. Additionally, male infants and infants with a 5-minute Apgar score <7 should be monitored carefully given their higher odds of pneumonia-associated death. The findings of this study can be used to emphasize prevention of pneumonia-associated deaths by considering the risk factors from this analysis during prenatal care.

Table 1. Summary of ICD-10 Codes, 2007-2010

ICD-10 Code	Description	% of Cases	Number of Infants
J12	Viral pneumonia, not elsewhere classified,	11.4	190
J13	Pnemonia due to *Streptococcus pneumoniae*	0.9	15
J14	Pneumonia due to *Haemophilius influenzae*	0.8	14
J15	Bacterial pneumonia, not elsewhere classified	12.4	208
J16	Pneumonia due to other infectious organisms, not elsewhere classified	0.0	0
J17	Pneumonia in diseases classified elsewhere	0.0	0
J18	Pneumonia, organism unspecified	76.1	1272

Table 2. Proportion of Selected Maternal and Infant Characteristics for Cases and Controls, United States, 2007-2010[+]

Characteristics	Cases N (%)	Controls N (%)	OR (95% CI)*
Total	1,671	6,684	
Sex			
Male	961 (57.5)	3,391 (50.7)	1.31 (1.18, 1.47)
Female	710 (42.5)	3,293 (49.3)	Reference
Birth Weight (grams)			
<2,500	607 (36.3)	425 (6.4)	8.40 (7.30, 9.66)
≥2,500	1,064 (63.7)	6,259 (93.6)	Reference
5-Minute Apgar Score			
<7	238 (14.2)	83 (1.2)	13.47 (10.42, 17.40)
≥7	1,395 (83.5)	6,552 (98.0)	Reference
Maternal Age (years)			
≤19	272 (16.3)	666 (10.0)	1.83 (1.54, 2.18)
20-24	579 (34.6)	1,646 (24.6)	0.86 (0.72, 1.02)
25-29	429 (25.7)	1,924 (28.8)	Reference
≥30	391 (23.4)	2,448 (36.6)	0.72 (0.62, 0.83)
Race			
White	1,078 (64.5)	5,155 (77.1)	Reference
Black	480 (28.7)	1,041 (15.6)	2.21 (1.94, 2.50)
AI/AN	49 (2.9)	80 (1.20)	2.93 (2.04, 4.21)
A/PI	64 (3.8)	408 (6.1)	0.75 (0.57, 0.98)
Maternal Marital Status			
Married	678 (40.6)	3,952 (59.1)	Reference
Unmarried	993 (59.4)	2,732 (40.9)	2.12 (1.78, 2.36)
Live Birth Order			
First	495 (29.6)	2,708 (40.5)	0.75 (0.66, 0.86)
Second	507 (30.3)	2,081 (31.1)	Reference
Third or more	657 (39.3)	1,849 (27.7)	1.46 (1.28, 1.66)

* OR: odds ratio, CI: confidence interval
[+] Maternal race is used to represent infant race and ethnicity in this study. AI/AN: American Indian/Alaska Native, A/PI: Asian/Pacific Islander

Table 3. Pneumonia-Associated Deaths and Infant Mortality Rates (IMRs) for Select Infant and Maternal Characteristics, United States, 2007-2010[+]

Characteristics	Weighted Deaths	Live Births	IMR	RR (95% CI)*
Total	1,734	16,122,069	10.7	
Sex				
Female	735	7,867,947	9.3	Reference
Male	999	8,254,122	12.1	1.3 (1.2, 1.4)
Birth Wight (grams)				
<2,500	627	1,034,839	60.6	8.3 (7.5, 9.1)
≥2,500	1,107	15,084,324	7.3	Reference
Maternal race				
White	1,117	12,416,170	9.0	Reference
Black	496	2,541,581	19.5	2.2 (2.0, 2.4)
A/PI	68	974,743	7.0	0.8 (0.6, 1.0)[p]
AI/AN	53	189,575	28.1	3.1 (2.4, 4.1)
5-Minute Apgar score				
<7	247	258,315	95.5	10.4 (9.1, 11.9)
≥7	1,447	15,762,357	9.2	Reference
Maternal age (years)				
≤19	284	1,651,678	17.2	1.8 (1.5, 2.1)
20-24	599	3,996,030	15.0	1.5 (1.4, 1.7)
25-29	443	4,555,056	9.7	Reference
≥30	408	5,919,305	6.9	0.7 (0.6, 0.8)
Maternal marital status				
Unmarried	1,032	6,591,690	15.7	2.1 (1.9, 2.3)
Married	703	9,530,379	7.4	Reference
Live birth order				
First	516	6,558,151	7.9	0.8 (0.7, 0.9)
Second	523	5,032,945	10.4	Reference
Third or more	682	4,431,568	15.4	1.5 (1.3, 1.7)

[+] IMR expressed as the weighted number of pneumonia-associated deaths per 100,000 live births

* RR: rate ratio, CI: confidence interval

[p] p-value: 0.0468

Table 4. Summary of Multivariable Logistic Regression Analysis of Select Risk Factors for Pneumonia-Associated Infant Deaths as Compared with Infant Survivors, United States, 2007-2010

Characteristic	OR (95% CI)*
Sex	
Female	Reference
Male	1.45 (1.28, 1.64)
5-Minute Apgar Score	
<7	7.41 (5.53, 10.01)
≥7	Reference
Maternal marital status	
Married	Reference
Unmarried	0.71 (0.62, 0.82)
Race	
White	Reference
Black	1.32 (1.14, 1.54)
A/PI	1.06 (0.78, 1.43)
AI/AN	2.23 (1.48, 3.31)
Birth Weight <2,500g	
Live Birth Order	
First	0.65 (0.46, 0.92)
Second	Reference
Third or more	1.35 (0.94, 1.93)
Maternal Age	
≤ 19	1.81 (1.14, 2.89)
20-24	1.84 (1.27, 2.65)
25-29	Reference
≥ 30	1.29 (0.90, 1.86)
Birth Weight ≥ 2,500g	
Live Birth Order	
First	0.45 (0.38, 0.54)
Second	Reference
Third or more	1.67 (1.41, 1.98)
Maternal Age	
≤ 19	2.47 (1.93, 3.16)
20-24	1.58 (1.31, 1.89)
25-29	Reference
≥ 30	0.55 (0.45, 0.67)

* OR indicates odds ratio; CI indicates confidence interval; AI/AN: American Indian/Alaska Native, A/PI: Asian/Pacific Islander

Figure 1

Distribution of Age at Death in Months
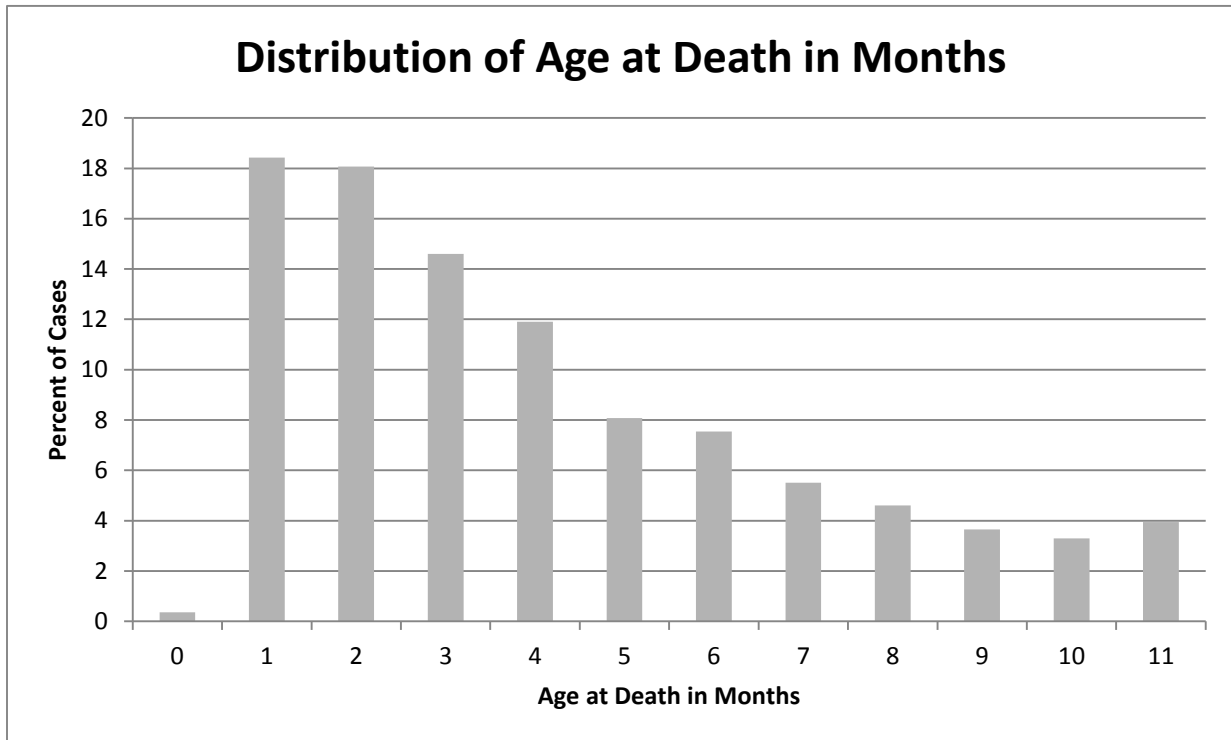
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