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Underlying and Multiple Causes of Death in Preterm Infants

Panagiota Kitsantas
George Mason University

Abstract: A limited number of studies have utilized multiple causes of death to investigate infant mortality patterns. The purpose of the present study was to examine the risk distribution of underlying and multiple causes of infant death for congenital anomalies, short gestation/low birth weight (LBW), respiratory conditions, infections, sudden infant death syndrome and external causes across four gestational age groups, namely $\leq 23, 24-30, 31-36, \geq 37$, and determine the extent to which mortality from each condition is underestimated when only the underlying cause of death is used. The data were obtained from the North Carolina linked birth/infant death files (1999 to 2003) and included 4908 death records. The findings of this study indicate that infants born less than 30 weeks old are more likely (odds ratio ranging from 1.99 to 6.03) to have multiple causes recorded when the underlying cause is congenital anomalies, respiratory conditions and infections in comparison to infants whose gestational age is at least 37 weeks. The underlying cause of death underestimated mortality for a number of cause-specific deaths including short gestation/LBW, respiratory conditions, infections and external causes. This was particularly evident among infants born preterm. Based on these findings, it is recommended that multiple causes, whenever available, should be studied in conjunction with the underlying cause of death data.

Key words: Infant mortality, multiple and underlying causes of death, preterm infants.

1. Introduction

Infant mortality data have been used to assess disease patterns and long-term trends, develop policies and design public health prevention and intervention programs. In most studies, mortality data analysis is conducted using the underlying cause of death which is defined as "the disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence, which produced the fatal injury" (National Center for Health Statistics, 2003)[1].

[1]National Center for Health Statistics. (2003). *NCHS definitions. Cause-of-Death.* Available at: http://www.cdc.gov/nchs/datawh/nchsdefs/list.htm.

Many concerns, however, have been raised over the years about the use of underlying cause of death as means of investigating and evaluating infant mortality. The use of the underlying-cause-of-death model ignores the role of other conditions and their contribution to death, and its reliability may be adversely affected as disease evaluation and coding tend to vary among physicians and other health providers (Nam *et al.*, 1989; Carver *et al.*, 1993). For instance, research has emphasized that the coding of disease classification (International Classification of Diseases, Ninth Revision, 1980) does not adequately measure the impact of short gestation on infant mortality (Carver *et al.*, 1993; Sowards, 1999), while others have suggested that the overall disease burden may have been underestimated due to the exclusive application of the underlying-cause-of-death model (Wall *et al.*, 2005; Redelings *et al.*, 2006). Consequently, researchers have addressed the potential use of multiple causes of death (Wall *et al.*, 2005; Redelings et al., 2006) and recommended that more attention should be given to the mode of identifying cause of death in studies and especially of those of infant mortality (Nam *et al.*, 1989).

Overall, in infant mortality studies, the extent to which the distribution of underlying and multiple causes of death differ across various gestational age groups has not been fully addressed. Given that infants born between 32-36 weeks are at higher risk for death during infancy (Kramer*et al.*, 2000) and their higher frequency of occurrence compared to those born at less than 32 gestational weeks (Gould *et al.*, 2000), it would be of interest to examine the frequency distribution and risk for one (underlying cause of death) versus multiple causes of infant death recordings associated with these gestational age groups and determine how they compare to infants born very preterm ($\leq$ 30 weeks) and full term ($\geq$ 37 weeks). Examining such differences may shed some light on the frequency and under-representation of specific causes of death by gestational age when only the underlying cause of death is utilized, and provide important information on the likelihood of multiple cause recordings for certain preterm infants.

The purpose of this exploratory study is (1) to examine the distribution of underlying and multiple causes of infant death for congenital anomalies, short gestation/low birth weight (LBW), respiratory conditions, infections, sudden infant death syndrome (SIDS) and external causes across four gestational age groups, namely $\leq$ 23, 24-30, 31-36, $\geq$ 37, and (2) identify those preterm infants that are at an elevated risk of having multiple cause recordings for a specific underlying cause of death using linked birth/infant death files from 1999 to 2003. Furthermore, to show the extent to which mortality from each condition is underestimated by using the underlying cause of death, frequencies for each of the four causes reported as mentions on the death certificate are compared with listings of these conditions when recorded as the underlying cause only.

2. Methods

The data were obtained from the North Carolina linked birth/infant death files from 1999 to 2003. This data set was made available by the North Carolina State Center for Health Statistics. The State Center provides a central collection site for birth records and infant mortality statistics. There were 4908 linked birth/infant death records. Infant deaths (defined as death between 0 and 364 days) were classified into six major categories, including congenital anomalies, short gestation/LBW, respiratory conditions, infections, SIDS and external causes (i.e., homicide, injuries, unknown causes, conditions originated in the perinatal period). They were classified according to the International Classification of Diseases, tenth revision (ICD-10) (National Center for Health Statistics, 2002). These causes of death were elected since they constitute some of the leading causes of infant mortality and they are frequently used in mortality data analyses. Gestational age classifications were as follows: $\leq$ 23, 24-30, 31-36 and $\geq$ 37 weeks. Classification of gestational age was based on findings and recommendations of previous studies that have examined the high risk of mortality and morbidity among premature infants (Kramer *et al.*, 2000).

Infant deaths were classified into two categories as having multiple causes of death (at least one non-underlying cause or mentions) and only one cause (underlying cause). Furthermore, in order to determine whether a specific condition has been underestimated when the underlying cause of death is used, each mention of the cause was compared to the listing of the condition as the underlying cause only.

Mortality frequencies and proportions were computed across the six causes and classifications of gestational age to compare cases with one underlying cause versus those with multiple causes, and determine the extent to which a specific cause is being underestimated by the use of underlying cause. Binary logistic regression was used and 95% confidence intervals are reported to examine the risk distribution for each gestational age group of having multiple causes versus one underlying cause. The analyses were performed using SPSS 13.0.

3. Results

Overall, 52.8% of the 4908 infant who died had multiple causes reported in addition to the underlying cause. The average number of causes per individual was 3.52 (lower quartile = 2.00, median = 4, upper quartile = 5). Table 1, which provides information on the frequency distribution and likelihood of cases with one versus multiple causes of death by gestational age, indicates that overall infants born between 24 to 30 weeks were approximately 3 times more likely to die of multiple causes in comparison to full term infants, and they had the highest

Table 1: Distribution of cases with only one cause (underlying cause) and multiple causes of death by gestational age.

	Cases with one cause		Cases with multiple causes		OR	95% CI
	n	%	*n*	%		
≤ 23	1131	48.8	613	23.6	0.53	(0.45, 0.61)
24-30	287	12.4	878	33.8	2.99	(2.53, 3.56)
31-36	242	10.5	430	16.6	1.73	(1.43, 2.09)
≥ 37	655	28.3	672	26.0	Reference	
Total	2315		2593			

Table 2: Underlying and multiple causes of death by gestational age) and multiple causes of death by gestational age.

Underlying cause of death	Cases with one cause		Cases with multiple causes		OR	95% CI
	n	%	*n*	%		
Congenital anomalies						
≤ 23	4	2.0	53	7.6	4.98	(1.76, 14.1)
24-30	20	9.7	106	15.3	1.99	(1.18, 3.36)
31-36	67	32.5	230	33.1	1.29	(0.91, 1.82)
≥ 37	115	55.8	306	44.0	Reference	
Total	206		695			
Short gestation/LBW						
≤ 23	744	87.5	76	58.0	0.21	(0.02, 2.28)
24-30	100	11.7	54	41.2	1.08	(0.96, 12.2)
31-36	4	0.5	0	0.0	–	
≥ 37	2	0.2	1	0.8	Reference	
Total	850		131			
Respiratory conditions						
≤ 23	35	37.0	83	22.6	2.61	(1.02, 6.69)
24-30	46	48.0	252	68.6	6.03	(2.42, 15.0)
31-36	3	3.2	22	6.0	8.07	(1.84, 35.4)
≥ 37	11	11.6	10	2.7	Reference	
Total	95		367			

Table 2 (continued): Underlying and multiple causes of death by gestational age) and multiple causes of death by gestational age.

Underlying cause of death	Cases with one cause		Cases with multiple causes		OR	95% CI
	n	%	*n*	%		
Infections						
≤ 23	8	13.6	41	19.0	2.76	(1.02, 7.48)
24-30	22	93.2	118	54.6	2.88	(1.31, 6.38)
31-36	15	25.4	31	14.4	1.11	(0.45, 2.73)
≥ 37	14	23.7	26	12.0	Reference	
Total	59		216			
SIDS						
≤ 23	0	0	0	0		
24-30	13	3.0	6	23.1	11.9	(3.90, 36.3)
31-36	85	19.6	7	27.0	2.12	(0.82, 5.48)
≥ 37	335	77.4	13	50.0	Reference	
Total	433		26			
External causes						
≤ 23	340	50.6	360	31.1	0.58	(0.46, 0.75)
24-30	86	12.8	342	29.5	2.27	(1.68, 3.06)
31-36	68	10.1	140	12.1	1.16	(0.82, 1.63)
≥ 37	178	26.5	316	27.3	Reference	
Total	672		1158			

number of multiple causes recorded on their death certificates. Although infants with a gestational age of 31-36 weeks experienced the least number of multiple causes (16.6%), they were still more likely (OR = 1.73) than term infants to have more than one cause reported. Furthermore, infants born at or less than 23 weeks were 0.53 times less likely compared to those born term to have additional causes recorded. This group also had the highest number (48.8%) of one cause (only underlying cause) recorded on their death certificate.

A further stratification by specific cause of death and gestational age (Table 2) revealed that infants born at 23 weeks or less were more likely (OR ranging from 2.61 to 4.98) to have multiple causes recorded when the underlying cause was congenital anomalies, respiratory conditions and infections in comparison to infants whose gestational age was at least 37 weeks. Similarly, infants with a gestational age of 24-30 weeks were far more likely (OR ranging from 1.99 to 6.03) to have multiple causes recorded compared to those born term for congenital

Table 3: Underlying cause of death as a percentage of mentions (multiple causes) by gestational age.

	Underlying cause		Mentions		Underlying cause as a percentage of mentions
n	%	n	%	%	
Congenital anomalies					
≤ 23	57	6.3	44	8.1	–
24-30	126	14.0	114	20.8	–
31-36	297	33.0	172	31.5	–
≥ 37	421	46.7	216	39.5	–
Total	901		546		–
Short gestation/LBW					
≤ 23	820	83.6	217	39.1	–
24-30	154	15.7	283	51.0	54.4
31-36	4	0.4	46	8.3	8.7
≥ 37	3	0.3	9	1.6	33.4
Total	981		555		–
Respiratory conditions					
≤ 23	118	25.5	191	23.7	61.7
24-30	298	64.5	448	55.6	66.2
31-36	25	5.4	85	10.6	29.4
≥ 37	21	4.6	81	10.1	26.0
Total	462		805		57.4
Infections					
≤ 23	49	17.8	52	27.5	94.2
24-30	140	51.0	47	24.8	–
31-36	46	16.7	42	22.3	–
≥ 37	40	14.5	48	25.4	83.4
Total	275		189		–
External causes					
≤ 23	700	38.3	266	15.3	–
24-30	428	23.4	644	37.0	66.5
31-36	208	11.4	328	18.8	63.4
≥ 37	494	30.0	500	28.7	98.8
Total	1830		1738		–

anomalies, respiratory conditions, infections and external causes. For respiratory related deaths, the odds ratio for cases having multiple causes increased with increasing gestational age.

The underlying-cause-of-death data captured only 8.7% of short gestation/LBW related deaths identified by multiple-cause records (mentions) for those born between 31-36 weeks, and 54.4% for infants with a gestational age of 24-30 weeks (Table 3). Respiratory related deaths were mostly underestimated by the use of the underlying cause which captured only 29.4% of cases reported in multiple-cause data for infants born between 31-36 weeks, and 26.0% for term infants. Furthermore, the percentage of deaths due to external causes relative to mentions was found to be moderate for 24-30 weeks (66.5%) and 31-36 weeks (63.4%). Deaths due to SIDS were not recorded as mentions for any of the other conditions or diseases. Congenital anomalies were declared as underlying causes more frequently on these death certificates than mentions. Overall, the underlying cause of death as a percentage of mentions was the highest for term infants compared to preterm across most of these major causes of infant mortality.

4. Discussion

Underlying and multiple cause data have been mainly employed to investigate various causes of death recorded on death certificates (Wall *et al.*, 2005; Redelings *et al.*, 2006) such as cancer (Richardson, 2006) and tuberculosis (Santo *et al.*, 2003). These applications clearly indicate that the multiple-cause-of-death model is superior to just using the underlying-cause-of-death data. Only a handful number of studies (Nam et al., 1989), however, have examined multiple cause frameworks of infant deaths. It is essential to indicate empirically any analytical benefits of using multiple causes of death (Nam at al., 1989), and the extent to which the underlying cause-of-death data underestimate mortality from specific diseases or conditions. Furthermore, the assessment of multiple and underlying causes of death in infants has become even more crucial as concerns have been raised over the contribution of preterm birth to infant mortality (Kramer et al., 2000), and the impact of classification systems on the process of finalizing the underlying cause of death.

In this study, the underlying cause of death underestimated mortality for a number of cause-specific deaths including short gestation/LBW, respiratory conditions, infections and external causes. This was particularly evident among infants born preterm. An under-representation of these causes due to the use of underlying cause of death may be problematic in the assessment of infant mortality or applications that utilize infant mortality data to study premature births and LBW (especially for those born between 24-30 weeks) and respiratory related problems. It also can affect prevention programs designed to prevent

deaths associated with such causes in premature infants.

Furthermore, whenever a respiratory condition was the underlying cause of death, the odds of frequent recording of multiple causes increased with gestational age. It is known that infants born at lower gestational ages have an increased frequency and severity of respiratory illness (Weisman, 2003). However, little is known about the contribution of respiratory illnesses associated with other conditions to mortality for specific gestational age groups such as those born at 31 weeks and above. Further research using multiple causes of death may warrant the relationship between gestational age and respiratory related deaths.

Overall, regardless of the specific cause of death, infants born at or less than 23 weeks of gestation were less likely to have multiple causes reported on their death certificates in comparison to full term infants. Further stratification by specific cause of death, however, revealed that they were more likely to experience multiple conditions compared to their term counterparts. This difference between the cumulative underlying-cause-of-death model (all causes of death) and the stratified one may be explained by the large number of recorded deaths due to external and short gestation/LBW related causes which masked the likelihood of recorded multiple conditions for this specific gestational age group. This indicates that researchers should explicitly select cause-specific-of-death models when investigating infant mortality since the recordings of other contributing causes to death may vary by the underlying cause of death.

Previous research has shown that the vast majority of deaths are attributable to complications of short gestation developed during the neonatal period (Swarz, 1990; Kliegman *et al.*, 1990). This may explain the large number of multiple causes recorded for preterm infants as they are more prone to develop other conditions and diseases which are likely to lead to death compared to term infants. This in turn complicates the analyses of causes of death for premature infants as the underlying cause of death may oversimplify the biological mechanisms of death for these infants. Consequently, researchers should carefully contemplate the analysis of multiple causes for premature infants since the underlying cause of death alone may not adequately reflect the contribution of other important conditions to mortality and morbidity.

There are some limitations, however, in using death certificate data. Death certificates are often imprecise and data are not rigorously evaluated (Nielsen et al., 1991). Variation also exists in opinions among individuals who are responsible for "coding" a condition or a disease and that can impact the accuracy of the classification system (Nam *et al.*, 1989; Carver *et al.*, 1993). Nonetheless, death certificate data are important in studying disease trends and patterns and can be used to prevent death. The few research studies that have been conducted on multiple and underlying causes of death suggest that multiple-causes-of-death

analyses can enrich and help define the mode of death more explicitly than the underlying-cause-of-death model. As Nam et al. (1989) indicate it is important for epidemiologists and public health officials to recognize and take into consideration that infant death can be the result of a number of causes rather than one cause. Based on the findings of this study, it is recommended that multiple causes are studied in conjunction with the underlying cause among premature infants and especially for those born between 32 and 36 weeks of gestational age. This can lead to better understanding of morbidity and mortality in infants and can assist in the development of more effective prevention and intervention programs targeting infant mortality.

References

Carver, J. D., McDermott, R. J., Jacobson, H. N., Sherin, K. M., Kanrek, K., Pimentel, B. and Tan, L. H. (1993). Infant mortality statistics do not adequately reflect the impact of short gestation. *Pediatrics* **92**, 229-232.

Gould, J. B., Benitz, W. E. and Liu, H. (2000). Mortality and time to death in very low birth weight infants: California, 1987 and 1993. *Pediatrics* **105**, 1-5.

World Health Organization (1980). *International Classification of Diseases*, Ninth Revision. World Health Organization, Geneva.

Kliegman, R., Rottman, C. J. and Behrman, R. E. (1990). Strategies for the prevention of low birth weight. *American Journal of Obstetrics and Gynecology* **162**, 1073-1083.

Kramer, M. S., Demissie, K., Yang, H., Platt, R. W., Sauve, R. and Liston, R. (2000). The contribution of mild and moderate preterm birth to infant mortality. *The Journal of American Medical Association* **284**, 843-849.

Nam, C. B., Eberstein, I. W., Deeb, L. C. and Terrie, E. W. (1989). Infant mortality by cuase: A comparison of underlying and multiple cause designation. *European Journal of Population* **5**, 45-70.

National Center for Health Statistics (1997-2004). *Data File Documentations, Multiple Cause-of-Death, 2000-2001.* National Center for Health Statistics.

Nielsen, G. P., Bjornsson, J. and Jonasson, J. G. (1991). The accuracy of death certificates. *Virchows Archives [A]* **419**, 143-146.

Redelings, M. D., Sorvillo, F. and Simon, P. (2006). A comparison of underlying cause and multiple causes of death: US vital statistics, 2000-2001. *Epidemiology* **17**, 100-103.

Richardson, D .B. (2006). Use of multiple cause of death data in cancer mortality analyses. *American Journal of Industrial Medicine* **49**, 683-689.

Santo, A. H., Pinheiro, C. E. and Jordani, M. S. (2003). Multiple-causes-of-death related to tuberculosis in the state of Sao Paulo, Brazil, 1998. *Revista de Saude Publica* **37**, 714-721.

Sowards, K. A. (1999). What is the leading cause of Infant mortality? A note on the interpretation of official statistics. *American Journal of Public Health* **89**, 1752-1754.

Swartz, M. (1990). Infant mortality: agenda for the 1990s. *Journal of Pediatric Health Care* **4**, 169-174.

Wall, M. M., Huang, J., Oswald, J. and McCullen, D. (2005). Factors associated with reporting multiple causes of death. *BMC Medical Research Methodology* **5**, 1-13.

Weisman, L. E. (2003). Population at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. *Pediatric Infectious Disease Journal* **22**, S33-S39.

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Panagiota Kitsantas
George Mason University
The College of Health and Human Services
Department of Health Administration and Policy, MS 1J3
4400 University Drive
Fairfax, VA 22030, USA
pkitsant@gmu.edu