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Estimating Neonatal Herpes Simplex Virus Incidence and Mortality Using Capture-recapture, Florida

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Abstract

Background.—Neonatal herpes simplex virus infection (nHSV) leads to severe morbidity and mortality, but national incidence is uncertain. Florida regulations require that healthcare providers report cases, and clinical laboratories report test results when herpes simplex virus (HSV) is detected. We estimated nHSV incidence using laboratory-confirmed provider-reported cases and electronic laboratory reports (ELR) stored separately from provider-reported cases. Mortality was estimated using provider-reported cases, ELR, and vital statistics death records.

Methods.—For 2011–2017, we reviewed: provider-reported cases (infants ≤ 60 days of age with HSV infection confirmed by culture or polymerase chain reaction [PCR]), ELR of HSV-positive culture or PCR results in the same age group, and death certificates containing International Classification of Disease, Tenth Revision, codes for herpes infection: P35.2, B00.0-B00.9, and A60.0-A60.9. Provider-reported cases were matched against ELR reports. Death certificates were matched with provider and ELR reports. Chapman's capture-recapture method was used to estimate nHSV incidence and mortality. Mortality from all 3 sources was estimated using log-linear modeling.

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Author contributions. J. M. conceptualized and designed the study; aided in data extraction, assisted in data cleaning, and performed final data analyses. He synthesized all analyses, wrote the initial draft of the manuscript, reviewed and revised the manuscript. S. D. B. conceptualized and designed the study, extracted data, prepared dataset for analysis, and performed initial data analyses. She revised and reviewed the final manuscript for critical content. J. A. S. and T. A. P. helped with conceptualization and design of the study including defining methodology and variables through their subject matter expertise. They aided in interpretation of the data and provide critical review and revision of draft and final manuscripts. J. H. added in the methodology for 3 source log-linear modeling of the data, performed analyses, and statistical testing pertaining to this study. He reviewed and revised the final manuscript for intellectual content. V. P. helped design the study, assisted in obtaining vital statistics data for analyses, aided in the visualization and interpretation of data, and critically reviewed and revised initial and final drafts of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious* Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Results.—Providers reported 114 nHSV cases, and ELR identified 197 nHSV cases. Forty-six cases were common to both datasets, leaving 265 unique nHSV reports. Chapman's estimate suggests 483 (95% confidence interval [CI], 383–634) nHSV cases occurred (31.5 infections per 100 000 live births). The nHSV deaths were reported by providers (n = 9), ELR (n = 18), and vital statistics (n = 31), totaling 34 unique reports. Log-linear modeling estimates 35.8 fatal cases occurred (95% CI, 34–40).

Conclusions.—Chapman's estimates using data collected over 7 years in Florida conclude nHSV infections occurred at a rate of 1 per 3000 live births.

Keywords

neonatal herpes; capture-recapture; surveillance; estimation

Genital herpes is one of the most prevalent sexually transmitted infections in the United States. In 2015–16, the prevalence among persons aged 14–49 was 47.8% for herpes simplex virus type 1 (HSV-1) and 11.9% for herpes simplex virus type 2 (HSV-2) [1]. These infections can be transmitted from a mother to newborn infant, most commonly during delivery [2]. Neonatal herpes infections cause substantial morbidity and have a high fatality rate, especially when infection is disseminated or involves the central nervous system (CNS). Even with the use of high dose acyclovir, case fatality rates remain high, approximately 30% for disseminated infection [2].

Despite the high case fatality rate, nHSV is not reportable in most states. It is reportable in Florida where healthcare providers are required to report nHSV infections, and clinical laboratories are required to report the detection of nHSV in specimens from individuals tested within 60 days of birth [3]. Prior to electronic lab reporting (ELR), provider reporting of reportable infectious diseases varied by disease (often tied with severity) and was often incomplete [4, 5]. One study found ELR identified over 4 times more reportable conditions than provider reporting of infectious diseases [6]. In Florida, laboratories began switching from paper reporting of labs to ELR in 2004, and the switch increased reporting by 3% to 51% depending on the laboratory [7]. In 2017, 580 of the largest laboratories or hospitals (out of an estimated 1166) were reporting laboratory results electronically, rather than via fax or mail (unpublished). Each source of reporting may be incomplete and the total number of cases may be underreported. Once cases are reported, provider and laboratory sources are often combined within a single event-based surveillance system for reporting incidence and mortality, but in Florida, these 2 reporting streams have remained separate independent sources for nHSV surveillance.

The incidence of nHSV in the United States and Canada (per 100 000 live births) has been estimated using a variety of sources including cases reported to surveillance systems (3.3–13.3/100 000), hospital discharge data (8.4–13.4/100 000), prospective or retrospective cohorts of pregnant women (31.2–41.5/100 000), and health information systems (5.1–60/100 000) [8–19]. Others have used national databases and models to estimate the burden of nHSV nationally and internationally [20, 21]. None of these studies used capture-recapture methods to compare cases from multiple data sources within the same jurisdiction.

Capture-recapture methods were first used to estimate the population size of wild animals. Using this method, a sample of animals was captured, tagged, and released to mix with the population. A second sample was captured and reviewed to see if any of the animals had been captured in the first sample. With some methodological assumptions regarding source independence, closed population, and capture homogeneity; the number captured in each sample and the number recaptured could then be used to estimate the total population, including those never captured. Similar principles have been applied to epidemiological studies of cases, conditions, or diseases found in multiple sources such as hospital records, registries, or death certificates to estimate the number of cases in a population [22–26]. The purpose of our analyses is to estimate the incidence of laboratory-confirmed nHSV in Florida using capture-recapture methods. For this we compared provider reported nHSV with ELR reported cases, determined the number reported by both, and estimated the total nHSV burden in Florida. We also used log-linear modeling, which allows the use of 3 different sample methods (death records, provider reported cases, and ELR cases) to estimate the total burden of fatal nHSV.

PATIENTS AND METHODS

Data Sources

Healthcare provider reports of nHSV were included if they included documentation of PCR or culture-confirmed HSV infection and were reported to the Florida Department of Health with a specimen collection date between 1 January 2011 and 31 December 2017. We excluded provider reports where the only lab evidence was an HSV antibody test.

Electronic laboratory reports to the Florida Department of Health come from over 200 laboratories and are stored in a separate ELR database from the sexually transmitted diseases (STD) surveillance system. We searched the ELR database for specimens collected between 1 January 2011 and 31 December 2017 using the Logical Observation Identifiers Names and Codes (LOINC) that have been used for herpes simplex virus according to the Public Health Information Network Vocabulary Access and Distribution System (PHIN VADS) downloaded on 10 February 2017 [27]. This list of 320 codes was further limited to the 92 codes containing “PCR” or “culture” in their description. Data were selected for persons whose date of birth was ≤ 60 days prior to specimen collection date and were de-duplicated, keeping the earliest positive specimen collection date.

The Florida Department of Health Vital Statistics (VS) database contains birth and death records for Floridians. Cases of nHSV identified by provider reports and by ELR were matched with the death records to compare (1) deaths among cases reported by providers, (2) deaths among cases ascertained by ELR, and (3) deaths attributed to nHSV that were not reported by providers or ELR. When matching deaths with provider or ELR reports, all causes of death were included in the search, but deaths were only considered to be due to nHSV if the death certificate had an infectious cause of death. (One death in an infant with laboratory-confirmed nHSV infection was excluded because it was an injury-related death.) To identify nHSV deaths among neonates not otherwise reported as having nHSV, death records were queried using International Classification of Disease, Tenth Revision, ICD-10, cause of death codes: P35.2 “congenital herpesviral infection,” B00.0-B00.9 “herpesviral

infections," and A60.0-A60.9 "anogenital herpesviral infections" for infants who died at age ≤ 60 days and were born between 1 January 2011 and 31 December 2017. Up to 20 ICD-10 codes can be listed on a death record. We attributed a death to nHSV if any of these codes were listed anywhere on the infant's death record or if a provider or ELR case had a death certificate with a nonspecific infectious cause of death. All data sources limited cases to those whose primary residence was Florida.

Variables, Matching, and Analysis

The variables we examined include: patient's name, mother's name, date of birth, specimen collection date, date of death (for VS data), HSV viral type, and vital status. ELR data do not contain vital status; it was obtained by matching ELR data to death records. Death records do not contain laboratory results, and ICD codes for HSV do not specify HSV type, so HSV type was not included in the analysis of deaths.

Provider and ELR case reports were matched using these variables: patient's name, date of birth, and mother's name. The death certificates were matched to provider and ELR case reports using these same variables. Cases were stratified by year of infection, viral type, and mortality outcome. For the 2-source morbidity analysis, we counted the number of cases reported by each source individually (provider and ELR), the number of reported cases that were common to both sources, and the number reported by either of the 2 sources. We then used Chapman's capture-recapture method [22] to estimate the total number of cases, including those missed by all sources. Total = [(provider reported cases + 1) × (ELR cases + 1)/(cases reported by both + 1)] -1. Wilson's method for binomial confidence intervals was used to determine 95% confidence limits for Chapman's estimates [28]. Moreover, we stratified these counts by report year, strain type, and vital status; and performed Chapman's capture-recapture for each of these stratifications. Rates per 100 000 live births were calculated using the total number of births reported for Florida between 2011 and 2017 (n = 1 534 140 in aggregate) [29]. The sum of the population estimates for Florida for each of these years was 137 639 534 [30].

For mortality analyses, we included a third source. Therefore, we counted deaths identified by each source, by 2 sources pairwise, and by all 3 data sources combined. We again used Chapman's capture-recapture method to estimate the total mortality cases based on any 2 data sources. Finally, 3-source estimates were generated using log-linear modeling using "Rcapture" package in R Statistical software (supplementary text) [31, 32]. The model incorporating temporal effects was the best fit model and therefore used to estimate the mortality of nHSV using 3 data sources (supplementary Table 2).

All data collected in provider and ELR databases were obtained through mandatory reporting as required of healthcare providers and laboratories by Florida statute. The project was reviewed by the Florida Department of Health Institutional Review Board (IRB) Office and classified as "exempt"; it was determined to be public health practice not research (IRB protocol number: 2019–009).

RESULTS

nHSV Incident Morbidity (Two Sources: Provider and ELR)

Over the 7-year study period, providers reported 114 laboratory-confirmed cases of nHSV (range: 10–25 cases per year) (Table 1). Over the same time frame, 197 unique reports of laboratory-confirmed HSV in infants aged ≤ 60 days were reported to a separate ELR database (range: 19–50 per year). Most of the provider-reported cases (68%) were missing information on herpes viral type. HSV viral type information was less likely to be missing for ELR-reported cases (28%). Combining both sources of report, there were more reports of nHSV2 (91) than nHSV1 (73). Case-fatality rates were similar for both reporting sources: 8% (9/114) for provider-reported cases and 9% (18/197) for ELR-reported cases. The age at time of specimen collection for laboratory-confirmed provider-reported cases was under 30 days for 94% (107) and under 42 days for 97% (111). Similarly, the age at time of specimen collection for ELR cases was under 30 days for 92% (181) and under 42 days for 97% (192).

Of the 114 provider-reported and 197 ELR-reported nHSV cases, 46 cases were reported by both sources (range: 2–12 per year) (Figure 1, pane 1). Merging data from the 2 sources improved data completeness for viral type for matched cases. For example, 3 provider-reported cases with unknown HSV type were matched with ELR cases that reported the type was HSV2. Overall, 265 unique nHSV cases were reported by either of the 2 sources, more than double the number of provider-reported cases.

The many cases contained in only 1 of the 2 databases (provider or ELR) suggests that some cases were not captured by either database. Using Chapman's method for capture-recapture, an estimated 483 (95% CI, 383–634) nHSV infections occurred in Florida from 2011 through 2017 (range: 41–96 per year). Considering only the fatal nHSV cases, an estimated 5 were missed by both sources using Chapman's method for capture-recapture. Nonfatal cases were more likely to be missed (220/490) than fatal cases (5/26). Thus, lowering the case fatality rate from 7.9% (21/265) among cases in either data source to 5.3% (26/490) among all cases estimated using capture-recapture.

Incidence rates of nHSV infection were lowest for provider-reported cases (7.4 nHSV cases per 100 000 live births [n = 114]) and were 73% higher for ELR-reported cases (12.8 per 100 000 live births [n = 197]). Combining cases reported by either provider reports or ELR yielded an incidence rate of 17.3 cases per 100 000 live births (n = 265). Finally, using Chapman's method to include those missed by both data sources, there were an estimated 31.5 nHSV infections per 100 000 live births (95% CI, 25.0–41.3) [n = 483].

nHSV Mortality (Three Sources: Provider, ELR, and Death Records)

All 9 laboratory-confirmed provider-reported nHSV deaths had matching records in the deaths database. There were 18 ELR-reported cases that matched with the death records (Table 2). There were 21 nHSV deaths reported by either reporting source, and 6 were reported by both. Of these, 10 were identified as viral type 2, 9 were an unknown viral type, and 2 were viral type 1. The cause of death was P35.2 "congenital herpesviral infection" or B0.0-B0.09 "herpesviral infections" for 7 (78%) of 9 provider-reported deaths and 15 (83%) of 18 ELR reported deaths. Of the 3 remaining fatal nHSV infections (2 were

reported by both sources), the first had cause of death listed as P23.9 “unspecified congenital pneumonia,” P29.0 “neonatal cardiac failure,” and P36.9 “bacterial sepsis of newborn, unspecified.” The second had R99 “ill-defined or unknown cause of death.” The third had P36.9 “bacterial sepsis of newborn, unspecified.”

A search of all death records using ICD-10 codes: P35.2 “congenital herpesviral infection” or B0.0-B0.09 “herpesviral infections” identified 13 deaths that were not otherwise reported as nHSV in addition to finding 18 of the previously described 21 nHSV deaths among cases reported by providers or ELR (Figure 1, pane 2). For the 31 fatal nHSV cases identified through death records, the cause of death was listed as P35.2 “congenital herpesviral infection” for 22, and B0.0-B0.09 “herpesviral infections” for 9; none were reported as A60.0–60.9 “anogenital herpesviral infections.” The 34 nHSV deaths identified using all 3 sources is much higher than the 26 estimated by using capture-recapture methods with provider reports and ELR (Table 2). Using death records for capture-recapture methods yielded estimates of 39 fatalities (95% CI, 23–79) (comparing provider reports and death records) and 37 fatalities (95% CI, 28–56) (comparing ELR and death records). Finally, using log-linear modeling, which considers data from all 3 sources, yielded an estimated 35.8 nHSV fatalities (95% profile likelihood CI, 34–40) (Table 2).

Because deaths were underreported, the nHSV fatality rates (per 100 000 live births) were low when estimated from provider reports (0.6), ELR (1.2), or both combined (1.4), compared to estimates from death records alone (2.0) or to those derived from the best fit log-linear model extrapolating cases and missing data from all 3 databases (2.3) (Table 2). The death rate from capture-recapture is nearly 4 times the rate from provider reports alone. Case fatality rates from different sources were similar, because sources both cases and deaths were underreported. The case fatality rate was 7.9% (9/114) for provider reported cases, 7.9% (21/265) for combined provider and ELR reported cases (without Chapman’s estimate for capture-recapture), and 7.5% (36/483) using capture-recapture estimates for the deaths and cases. This last estimate, 7.5% (36/483), is higher than our earlier estimate, 5.3% (26/490), that did not include nHSV identified only in the death certificate database.

DISCUSSION

Provider reporting, electronic laboratory reporting, and vital statistics were incomplete sources for estimating nHSV morbidity and mortality in Florida. Using all 3 sources in combination greatly increased the completeness of case and death ascertainment in Florida. However, capture-recapture estimates suggest that there were many additional cases and some deaths that were not reported by any source.

The nHSV case rates from single reporting sources in Florida were similar to rates from other single source surveillance and hospital discharge data studies [8, 10]. Combining both provider reports and ELR led to a slightly higher rate than that observed in other surveillance studies that combined reporting sources [9, 11, 13, 14, 18, 33]. Our capture-recapture estimate was substantially higher than model estimates based on surveillance [21] because capture-recapture methods include an estimate of unreported cases. Our capture-recapture estimate was nearly identical to the rate seen in a prospective cohort study of pregnant

women from Washington state (31.2 infections per 100 000 live births) [15] and lower than a retrospective longitudinal cohort study (41.5 per 100 000 live births) [19] where case reporting would be expected to be more complete than passive surveillance. One potential reason for discrepancies between surveillance and our model is some cases are diagnosed but not reported [6, 7]. A previous assessment of surveillance in 9 states found existing surveillance was an unreliable way of assessing the burden of disease [8].

The strength of capture-recapture is the ability to estimate the number of cases that are underreported by existing surveillance systems. The chief weakness is that those estimates can be biased when reporting sources are not independent [22]. We found little overlap in reporting between provider reports and ELR. If anything, ELR reporting might reduce provider-reporting if providers know that the health department already receives notification from the testing laboratory. In terms of mortality from nHSV, there was some dependency between ELR reported cases and death records because ELR cases were used to search death records. However, a death among cases documented solely by ELR reports would not have to contain the queried ICD-10 codes to be considered a death due to nHSV. Our study and the NYC study found P35.2 “congenital herpesviral infection” was the most commonly reported code and neither study identified a case using codes A60.0-A60.9 “anogenital herpesviral infections” [34]. However, nHSV deaths with codes B00.0-B00.9 “herpesviral infections” in Florida were 3 times that of those identified in New York City. Finally, a death solely identified through ICD-10 codes on death records (n = 13 in our study) could have been misclassified as related to nHSV if maternal lesions were listed on an infant’s death record.

Capture-recapture estimates can also be biased if there are changes in the population [22]. In this study, it was not possible to control for the infants entering or leaving Florida. However, given the 60-day age limit for the case definition the impact on our estimates should be small. Similarly, births varied by <6% over study period (212 954 in 2012 to 225 018 in 2016), so changes had minimal impact on our estimates [29]. Although this study has highlighted the impact of nHSV mortality, we did not address the impact from nHSV morbidity.

The substantial underestimate in reported nHSV cases and deaths revealed by this analysis may raise questions about the accuracy of passive surveillance. Other studies have found similar underreporting for other conditions and adjusted reported counts to better estimate the true burden of disease [35–37].

CONCLUSION

Provider reporting and ELR reporting both substantially underestimated nHSV morbidity and mortality in Florida. Capture-recapture estimates and log-linear modeling suggest the incidence could be more than 80% higher (483 estimated cases compared to 265 reported cases), and the mortality rate more than 70% higher (35.8 estimated deaths compared to 21 deaths) than that estimated from provider and ELR reporting combined. Future nHSV surveillance efforts should focus on reducing the number of cases that are not reported. Expanding ELR to all laboratories could identify all positive tests. Encouraging providers

to report nHSV cases could help identify cases not reported by ELR and add valuable information not available in laboratory reports. Incorporating death certificate data into routine surveillance practices could aid in identifying nHSV deaths. If surveillance systems are improved, few cases will be not reported, and capture-recapture methods will no longer be needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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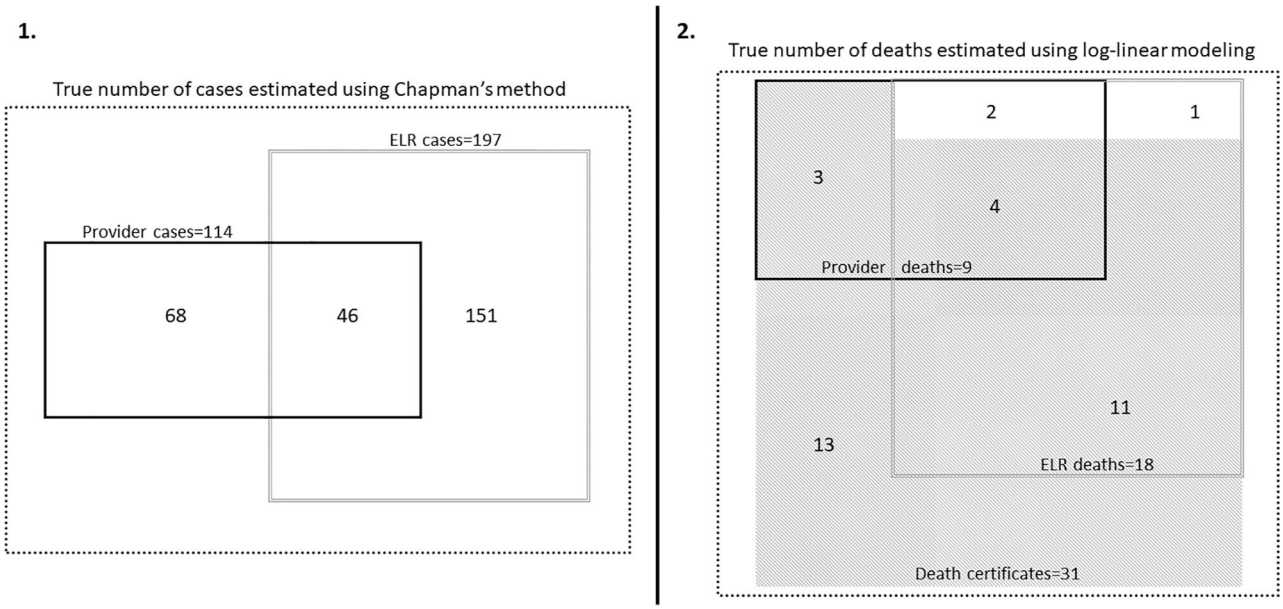

Figure 1.

Pane 1. Neonatal herpes cases from provider reports (*black line*) and ELR reports (*gray double line*) in relation to Chapman's capture-recapture estimate (*dotted line*). **Pane 2**. Deaths from provider-reported deaths (*black line*), ELR-reported deaths (*gray double line*), and death certificates (*gray object*); in relation to log-linear modeling estimates (*dotted line*). Abbreviation: ELR, electronic laboratory report.

Table 1.

Reports of Neonatal Herpes Simplex Virus Infections Reported by Providers, Electronic Laboratory Reports (ELR), and Capture-recapture Estimated Total Number of Cases, Including Those Not Reported, Florida, 2011–2017

	Provider Cases	ELR Cases	Matched Cases	Non-Matched Cases	Both Sources Combined	Chapman's Estimator[a]	95% CI
Total	114	197	46	219	265	483	383–634
Rate per 100 000 live births	7.4	12.8	N/A	N/A	17.3	31.5	25.0–41.3
Year							
2011	10	19	2	25	27	72	32–341
2012	11	21	2	28	30	87	38–415
2013	25	20	5	35	40	90	53–223
2014	21	27	12	24	36	46	33–76
2015	17	32	8	33	41	65	40–128
2016	12	28	8	24	32	41	25–79
2017	18	50	9	50	59	96	58–184
Viral type[b]							
1	18	59	14	59	73	75	50–122
2	18	82	21	70	91	71	50–103
Unknown	78	56	11	90	101	374	245–688
Death							
Yes	9	18	6	15	21	26	16–55
No	105	179	40	204	244	464	362–623

Abbreviation: CI, confidence interval.

[a]Chapman's capture-recapture method was used to estimate totals for each line, so subgroup totals will not add up to 483.

[b]For some cases, viral type was reported by one source but not the other. In these instances, we used the known strain type in the matched value lowering the unknown values.

Table 2.

Reported Neonatal Herpes Simplex Virus Deaths by Reporting Source (Provider Report, Electronic Laboratory Report (ELR), and Death Records, Florida, 2011–2017

		Death Records	
Provider Report	**ELR**	**Yes**	**No**
Yes	Yes	4	2
	No	3	0
No	Yes	11	1
	No	13	0
Total deaths from different reporting sources and estimates			
	Counts	95% CI	Rate per 100 000 Live Births
Reported by:			
Provider	9	N/A	0.6
ELR	18	N/A	1.2
Provider or ELR	21	N/A	1.4
Death records	31	N/A	2.0
Any of the above	34	N/A	2.2
Estimated deaths:			
Chapman's estimator (provider-ELR)	26	16–55	1.7
Chapman's estimator (provider-death records)	39	23–79	2.5
Chapman's estimator (ELR-death records)	37	28–56	2.4
Three source log-linear modeling	35.8	34–40	2.3

Abbreviations: CI, confidence interval; N/A, not applicable.