Evidence Suggests a Decrease in the Incidence of Kernicterus in California

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We identified children diagnosed with kernicterus in the California Department of Developmental Services and estimated an incidence of 0.42 per 100 000 births from 1988 to 2014, significantly decreasing to 0.04 per 100 000 births after 2009. We also examined national infant kernicterus mortality from 1979 to 2016 using CDC data. It did not decrease significantly. *(J Pediatr 2023; ■:1-4).*

Kernicterus, a rare and devastating disease that can arise from untreated extreme neonatal hyperbilirubinemia, was deemed a "serious reportable event" by the National Quality Forum in 2002.[1] The American Academy of Pediatrics (AAP) published clinical practice guidelines for neonatal hyperbilirubinemia in 1994 and 2004[2,3] and an unofficial update with clarifications in 2009 that promoted universal newborn bilirubin screening.[4] Universal screening was reaffirmed in the AAP 2022 hyperbilirubinemia clinical practice guideline revision.[5]

Monitoring kernicterus incidence is important for assessing interventions (such as universal newborn bilirubin screening) aimed at minimizing hyperbilirubinemia-related injuries. Data from the California Perinatal Quality Care Collaborative (CPQCC; a statewide network of neonatal intensive care units and high-risk infant follow-up clinics focused on quality improvement) suggests that extreme (≥25 mg/dL) hyperbilirubinemia peaked in California in 2009 and declined significantly thereafter,[6] but whether there have been statewide changes in kernicterus incidence is unknown, largely because of its rarity.

In 2011, Brooks et al reported annual California kernicterus incidence estimates for birth years 1988-1997 using data from the California Department of Developmental Services (CDDS) and national infant kernicterus mortality using Centers for Disease Control and Prevention data from years 1979-2006.[7] This article updates incidence estimates and death rates through 2014 and 2016, respectively, and assesses potential effects of the CPQCC quality improvement initiative[6] and publication of the update to the AAP's hyperbilirubinemia treatment guidelines in 2009.[4]

Methods

We applied the same methods used in our 2011 study.[7] California children with developmental disabilities are eligible to receive treatment coordinated by the CDDS; eligibility criteria for the CDDS did not change over the course of the study period. We identified children with kernicterus from the CDDS database using physician-recorded *International Classification of Diseases* (ICD) diagnostic codes on the annually updated Client Development Evaluation Report (CDER): ICD-9: 773.4, Kernicterus due to isoimmunization; 774.7, Kernicterus not due to isoimmunization; ICD-10: P57.0, Kernicterus due to isoimmunization; P57.8, Other specific kernicterus; and P57.9, Kernicterus, unspecified. The items on the CDER forms have been externally validated and have been deemed satisfactory.[8]

We searched for any diagnosis (ie, not just primary) with these codes on CDERs completed through 2019, the last year for which data were available, to assess incidence in 1988-2014. This allowed at least 5 years from birth for case ascertainment.

Incidence was calculated as the total number of kernicterus cases with each year of birth divided by the number of California live births that year, as reported by the California Health and Human Services Agency.

National infant kernicterus deaths were identified in the Center for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (WONDER) compressed mortality database using the same ICD, Ninth Revision, and ICD, Tenth Revision, codes. Infant mortality was assessed until 2016, the last year for which WONDER compressed mortality data were available.

CIs and statistical hypothesis tests were calculated assuming the counts followed a Poisson distribution. This study was approved by the institutional review boards for the University of California–San Francisco and California State.

Details on potential missing cases and descriptive characteristics of the CDDS kernicterus cases from birth years 1988-1997 were provided in the previous article.[7]

AAP	American Academy of Pediatrics
CDDS	California Department of Developmental Services
CDER	Client Development Evaluation Report
CPQCC	California Perinatal Quality Care Collaborative
ICD	*International Classification of Diseases*
WONDER	Wide-ranging Online Data for Epidemiologic Research

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Results

CDDS data identified 62 children with kernicterus (46 male, 16 female) born in years 1988-2014, for an overall incidence of approximately 0.42 (95% CI 0.32-0.54) per 100 000 California live births. The 5-year moving average of kernicterus incidence is shown in **Figure 1**, and annual incidence is shown in **Table I** (available at www.jpeds.com). We identified 2 additional cases born in 2015, although they were excluded from our primary analysis because their follow-up was less than 5 years.

There was no significant difference before and after the publication of the 1994 AAP guideline (1988-1993 vs 1995-2014; $P = .92$), although the incidence significantly declined to 0.04 per 100 000 after the 2009 clarifications (1988-2008 vs 2010-2014; $P = .002$) and a test for linear trend showed a significant decrease over time ($P = .009$). Supplementary analyses that included the 2 additional children born in 2015 did not produce materially different results.

According to their ICD codes, isoimmunization caused 10 of 62 cases of kernicterus in the CDDS. Of these, 2 were born in 1988, 1 in 1989, 1 in 1990, 1 in 1995, 2 in 2000, 2 in 2001, and 1 in 2007.

There were 39 infant deaths due to kernicterus (31 male; 8 female) nationally between 1979 and 2016, for an overall crude death rate of 0.26 per million live births (**Table II**). The death rate was 0.25 per million during 2010-2016, not significantly lower than in 1979-2009 (0.26 per million).

Discussion

The CDDS data suggest that California kernicterus incidence is low. Accounting for approximately 10% early mortality[9] yields an adjusted incidence of 0.47 per 100 000 live births. Our results indicate the incidence was particularly low during 2010-2014. This period followed the 2009 publication of unofficial clarified guidelines and commentaries recommending universal bilirubin screening.[4,10] Universal bilirubin screening was associated with an increase in phototherapy use and a reduction in incidence of severe (20-24.9 mg/dL) and extreme (≥25 mg/dL) hyperbilirubinemia in Northern California Kaiser hospitals.[11] Data from the CPQCC, which collects data on more than 90% of the state's neonatal intensive care units and advocates for universal bilirubin screening,[6,12] demonstrated that the incidence of extreme neonatal hyperbilirubinemia in California peaked in 2009 and significantly declined thereafter.[6] The lower kernicterus incidence figure we calculated after 2009 (0.04 per 100 000) may be a direct result of decreasing neonatal extreme hyperbilirubinemia rates in California.

Although the California incidence data may not be generalizable to the entire US, as evidenced by the time period's relatively stable national kernicterus death rate, the reduction in extreme hyperbilirubinemia incidence after implementation of universal bilirubin screening was replicated in a system of 116 hospitals across the US.[13] National kernicterus death rates may decrease with the release of newer data

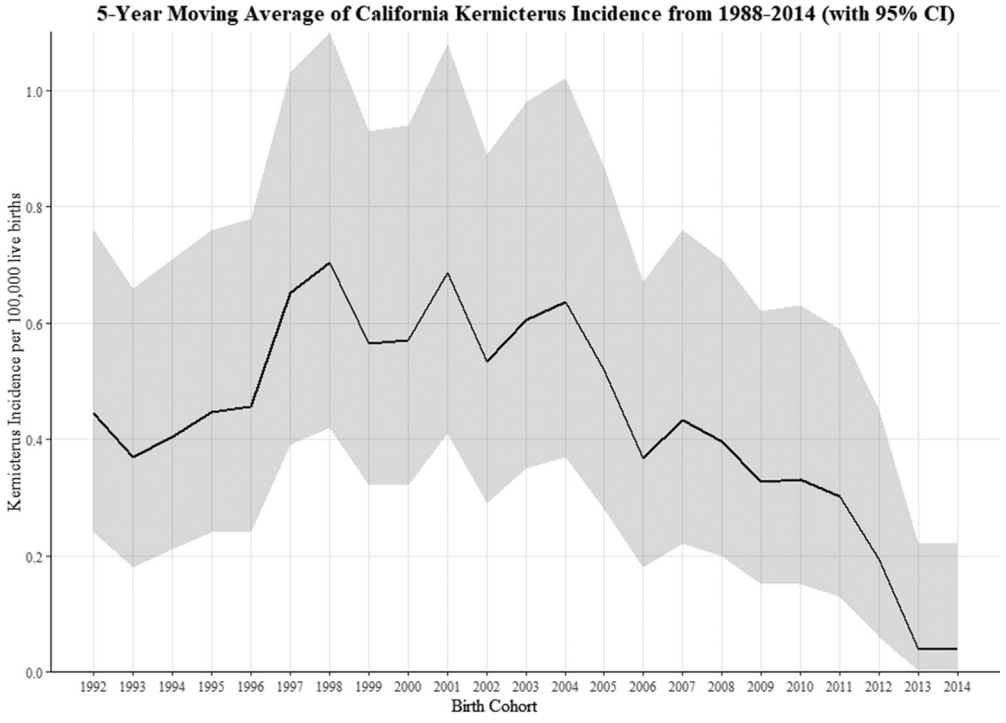

Figure 1. 5-year moving average of California kernicterus incidence, 1988-2014. The average is of the year presented on the x-axis and the 4 preceding years. For example, the rightmost value corresponds to the average within years 2010-2014.

Table II. US kernicterus infant (<1 year) mortality, 1979-2016

Years of death	Kernicterus deaths			Total live births	Crude death rate per million live births (95% CI)
	Male	Female	Total		
1979	1	1	2	3 494 398	0.57 (0.28-2.07)
1980	2	0	2	3 612 258	0.55 (0.27-2.00)
1981	1	0	1	3 629 238	0.28 (0.08-1.54)
1982	0	2	2	3 680 537	0.54 (0.26-1.96)
1983	1	0	1	3 638 933	0.27 (0.08-1.53)
1984	0	1	1	3 669 141	0.27 (0.08-1.52)
1985	1	0	1	3 760 561	0.27 (0.08-1.48)
1986	0	0	0	3 756 547	0.00 (0.00-0.98)
1987	0	0	0	3 809 394	0.00 (0.00-0.97)
1988	0	0	0	3 909 510	0.00 (0.00-0.94)
1989	0	0	0	4 040 958	0.00 (0.00-0.91)
1990	0	0	0	4 158 212	0.00 (0.00-0.89)
1991	0	0	0	4 110 907	0.00 (0.00-0.90)
1992	1	0	1	4 065 014	0.25 (0.07-1.37)
1993	2	0	2	4 000 240	0.50 (0.24-1.81)
1994	1	2	3	3 952 767	0.76 (0.44-2.22)
1995	0	0	0	3 899 589	0.00 (0.00-0.95)
1996	0	0	0	3 891 494	0.00 (0.00-0.95)
1997	1	0	1	3 880 894	0.26 (0.07-1.44)
1998	2	0	2	3 941 553	0.51 (0.24-1.83)
1999	2	0	2	3 795 762	0.53 (0.25-1.90)
2000	1	0	1	3 805 648	0.26 (0.08-1.46)
2001	2	0	2	4 012 658	0.50 (0.24-1.80)
2002	2	0	2	3 951 461	0.51 (0.24-1.83)
2003	2	0	2	3 975 871	0.50 (0.24-1.82)
2004	0	1	1	4 014 258	0.25 (0.07-1.39)
2005	2	0	2	4 004 393	0.50 (0.24-1.80)
2006	0	0	0	4 041 738	0.00 (0.00-0.91)
2007	0	0	0	4 147 997	0.00 (0.00-0.89)
2008	0	0	0	4 132 735	0.00 (0.00-0.89)
2009	1	0	1	4 003 587	0.25 (0.07-1.39)
2010	0	0	0	3 944 153	0.00 (0.00-0.94)
2011	1	0	1	3 996 537	0.25 (0.07-1.39)
2012	1	0	1	3 943 077	0.25 (0.07-1.41)
2013	2	0	2	3 941 783	0.51 (0.24-1.83)
2014	0	0	0	3 948 350	0.00 (0.00-0.93)
2015	1	0	1	3 978 038	0.25 (0.07-1.40)
2016	1	1	2	3 970 145	0.50 (0.24-1.82)
1979-2009	25	7	32	120 788 253	0.26 (0.18-0.37)
2010-2016	6	1	7	2 722 083	0.25 (0.10-0.52)
Total	31	8	39	148 510 336	0.26 (0.23-0.36)

that reflects universal bilirubin screening's integration into more US hospitals.

Our estimate of the adjusted incidence of 0.47 per 100 000 California live births is much lower than the 1.2 and 1.3 per 100 000 reported in Denmark and Sweden, respectively.[14,15] One reason for our lower figure is the potential underreporting of milder cases, for instance, those with "auditory-predominant" kernicterus,[16] who may not qualify for CDDS services. For comparison, 5 of the 12 kernicterus cases identified in Denmark during 2000-2015 were considered "auditory kernicterus spectrum disorder."[14]

On the other hand, our case ascertainment may be more complete as the CDDS allowed us to identify children diagnosed with kernicterus later than was possible in other studies.[15] Only 73% of CDDS cases were ascertained by age 5 years (**Figure 2**; available at www.jpeds.com), later than one would expect clinically significant kernicterus to be identified—this may suggest that kernicterus ascertained after age 5 years could either be milder cases or children moving into California. Given the added incentive of California's provision of free services to children with developmental disabilities, any potential effect of late enrollment would lead to overestimation of kernicterus incidence.

Because CDERs are completed annually, our investigation can mitigate the misclassification of kernicterus found in other studies.[15] Kernicterus diagnoses proved to be extremely reliable in our data—among cases with at least 2 completed CDERs, all but 1 (98%) had kernicterus ICD codes marked on multiple CDERs.

Kernicterus has been labeled a "never event," and although these data indicate that kernicterus has become very rare in California, further reductions may be more difficult. In particular, eliminating cases due to glucose-6-phosphate dehydrogenase

deficiency will be challenging because even if we screened for glucose-6-phosphate dehydrogenase deficiency,[17,18] severe acute hemolysis can occur even when all known triggers are scrupulously avoided.

It is difficult to determine whether AAP guidelines, universal bilirubin screening practices, or the CPQCC quality improvement initiative have improved prevention efforts, though the data presented here document decreases in incidence in recent years and mirror the decrease of severe neonatal hyperbilirubinemia incidence in California hospitals since 2009. Although this is reassuring, sustained monitoring of kernicterus is needed for periodic reassessment of the impact of evolving hyperbilirubinemia treatment guidelines. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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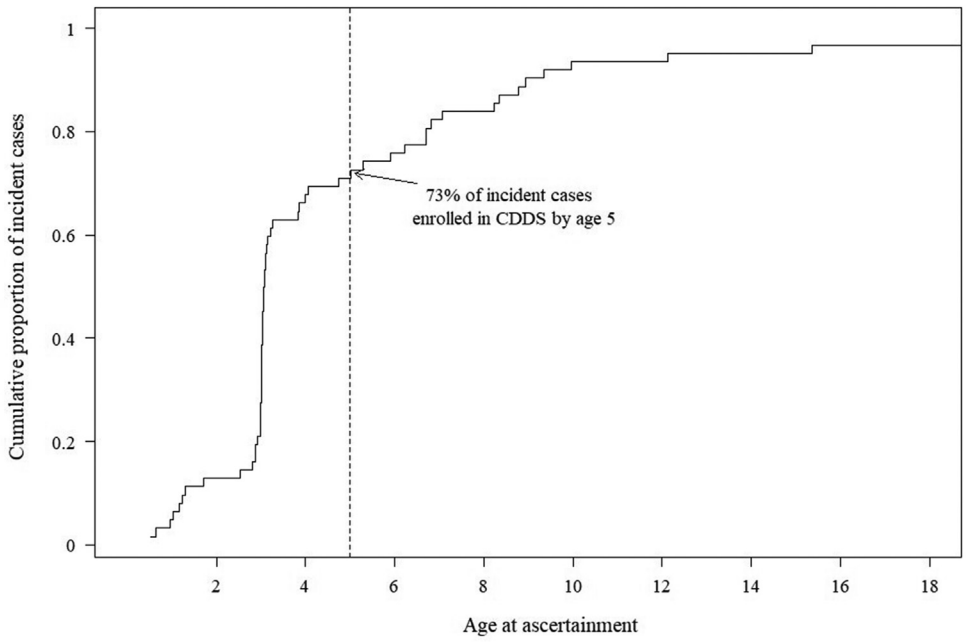

Figure 2. Age of kernicterus ascertainment in the CDDS, birth years 1988-2014.

Table I. California kernicterus incidence by birth year, 1988-2014

Birth years	Kernicterus incidence			California live births	Kernicterus incidence per 100 000 California live births (95% CI)
	Male	Female	Total		
1988	2	2	4	532 708	0.75 (0.20-1.92)
1989	3	1	4	569 308	0.70 (0.19-1.80)
1990	2	0	2	611 666	0.33 (0.04-1.18)
1991	2	0	2	609 228	0.33 (0.04-1.19)
1992	1	0	1	600 838	0.17 (0.00-0.93)
1993	2	0	2	584 483	0.34 (0.04-1.24)
1994	3	2	5	567 034	0.88 (0.29-2.06)
1995	3	0	3	551 226	0.54 (0.11-1.59)
1996	1	1	2	538 628	0.37 (0.04-1.34)
1997	4	2	6	524 174	1.14 (0.42-2.49)
1998	2	1	3	521 265	0.58 (0.12-1.68)
1999	1	0	1	518 073	0.19 (0.00-1.08)
2000	3	0	3	531 285	0.56 (0.12-1.65)
2001	3	2	5	527 371	0.95 (0.31-2.21)
2002	2	0	2	529 241	0.38 (0.05-1.37)
2003	4	1	5	540 827	0.92 (0.30-2.16)
2004	1	1	2	544 685	0.37 (0.04-1.33)
2005	0	0	0	548 700	0.00 (0.00-0.67)
2006	1	0	1	562 157	0.18 (0.00-0.99)
2007	3	1	4	566 137	0.71 (0.19-1.81)
2008	2	2	4	551 567	0.73 (0.20-1.86)
2009	0	0	0	526 774	0.00 (0.00-0.70)
2010	0	0	0	509 979	0.00 (0.00-0.72)
2011	0	0	0	502 023	0.00 (0.00-0.73)
2012	1	0	1	503 788	0.20 (0.01-1.11)
2013	0	0	0	494 392	0.00 (0.00-0.75)
2014	0	0	0	502 973	0.00 (0.00-0.73)
1988-1997	23	8	31	5 689 293	0.54 (0.37-0.77)
1998-2014	23	8	31	8 981 237	0.35 (0.23-0.49)
Total	46	16	62	14 670 530	0.42 (0.32-0.54)