Trends in Intussusception-Associated Deaths among US Infants from 1979-2007

Rishi Desai, MD, MPH, Aaron T. Curns, MPH, Manish M. Patel, MD, and Umesh D. Parashar, MBBS, MPH

Objective We examined data from 1979-2007 to generate up-to-date baseline estimates of rotavirus intussusception mortality in US infants, to inform policy deliberations of the risks and benefits of vaccination.

Study design Secular trends in the infant intussusception mortality rate were evaluated using national multiple cause-of-death and natality data from 1979- 2007. Linked birth/infant death data from 1998-2006 were examined to identify risk factors for intussusception deaths.

Results After declining from 1979-1996, the average annual intussusception mortality rate stabilized from 1997-2007 at 2.1 per 1 million live births (range, 1.0-3.0). In multivariate analysis, significant variables associated with intussusception deaths included no prenatal care (OR, 5.4; 95% CI, 1.9-15.4) and birth order (≥3rd) (OR, 2.4; 95% CI, 1.4-4.4 [reference: birth order (1st)]).

Conclusions Given the annual variation in intussusceptions mortality and low baseline rates, if a low vaccine-associated risk of death from intussusception exists in the United States, it would be difficult to assess using intussusception mortality trend data alone. Factors associated with intussusception mortality risk may be related to delayed or reduced health care access. *(J Pediatr 2012;160:456-60)*.

Approximately two-thirds of all intussusceptions occur among infants <1 year old, with the peak incidence occurring at 3-6 months of life.[1,2] Some reduce spontaneously, but most require hospitalization with treatment by either ultrasound-guided hydrostatic reduction or surgical reduction.[2-5]

In 1998, the Advisory Committee on Immunization Practices recommended the use of a tetravalent rotavirus vaccine (RRV-TV) in the United States.[6] However, within 1 year of vaccine introduction, an excess risk of approximately 1 intussusception in 10 000 RRV-TV vaccinees was identified in postlicensure studies.[7,8] In response, the Advisory Committee on Immunization Practices recommended withdrawal of RRV-TV, and by November 1999, US infants were no longer routinely vaccinated against rotavirus.[9]

Since 2006, 2 new rotavirus vaccines have been licensed and recommended for routine use in US infants: a monovalent RV vaccine (RV1) and pentavalent rotavirus vaccine (RV5).[10,11] Combined, RV1 and RV5 underwent prelicensure trials of >120 000 infants, which did not demonstrate an association of either vaccine with intussusceptions.[12,13] However, postlicensure evaluations conducted in Latin America and Australia have recently identified a possible risk of intussusception with both vaccines occurring within the first 7 days after vaccination,[14,15] at a rate lower (1 in 50 000 to 100 000 vaccinees) than that with RRV-TV (1 in 5000-10 000 vaccinees).[8]

To date, US studies have found no excess risk of intussusception following rotavirus vaccination[16,17]; however, data from other countries have prompted a discussion regarding the potential risks versus benefits of vaccination. In addition to hospitalization and surgery from vaccine-associated intussusception, there is also concern about mortality from vaccine-associated intussusception, given that relatively few US infants die from rotavirus.[18]

Because intussusception mortality in US infants was last assessed in 1997,[19] we examined data from 1998-2007, the most recent year with available mortality data, to generate up-to-date baseline prevaccine estimates against which trends after vaccine introduction can be compared.

Methods

The National Center for Health Statistics (NCHS) US Multiple Cause-of-Death data[20] for 1979-2007 and the US Period Linked Birth/Infant Death data[21] for 1998-2006 were examined. The Multiple Cause-of-Death data include all death records in the US. The Linked Birth/Infant Death data includes all US live births occurring each year,

ICD-10	*International Classification of Diseases, Tenth Revision*
NCHS	National Center for Health Statistics
RR	Relative risk
RRV-TV	Tetravalent rotavirus vaccine
RV1	Monovalent RV vaccine
RV5	Pentavalent rotavirus vaccine

From the Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA

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and for the subset of infants who die within the first year of life, the information from the birth certificate and death certificate are linked. Intussusception-associated deaths among infants were defined as deaths for which the *International Classification of Diseases, Ninth Revision*[22] code 560.0 or *International Classification of Diseases, Tenth Revision* (ICD-10)[23] code K56.1 (implemented in 1999) was listed anywhere on the death record.

The NCHS US natality data[24] for 1979-2007 were used to provide denominators to calculate intussusception mortality rates per 1 million live births for specific years. Finally, a random sample was obtained of approximately 0.1% of infant survivors, those infants who survive the first year of life, from the Linked Birth/Infant Death database born between 1998 and 2006, and birth certificate characteristics of these infants were compared with those who died from intussusception.

Data Analysis

Multiple cause-of-death and natality data were used to calculate annual intussusception deaths and mortality rates per 1 million live births from 1979-2007. Mortality rates were also calculated by age group, sex, race, and birth region. Comparisons of rates were made by using χ^2 tests. For all intussusceptions-associated deaths, month-of-age at death was categorized as 0-2, 3-5, 6-8, or 9-11 months, and location of death was categorized as in-hospital or community.

The 1998-2006 Linked Birth/Infant Death database was used to analyze intussusception-associated infant deaths and survivor infant data by birth and maternal characteristics. Prenatal care adequacy was defined using the modified Institute of Medicine (Kessner) index,[25,26] which includes month prenatal care began, number of prenatal visits, and infant gestation. Variables that were significantly associated ($P < .05$) with intussusception-associated death in univariate analysis were further analyzed by fitting a series of stepwise logistic regression models. ORs with 95% CIs were calculated by using logistic regression analysis.

Results

Overall Trends and Epidemiology in Intussusception Mortality from 1979-2007

From 1979-2007, 410 intussusception-associated infant deaths were reported, yielding an overall average annual mortality rate of 3.7 per 1 million live births. Intussusception-associated mortality fell from 8.3 per 1 million live births in 1979 to 2.1 per 1 million in 1996 ($P < .001$) and then remained stable from 1997-2007 at an average of 2.1 per 1 million live births (range, 1.0-3.0) ($P = .77$) (Figure 1). In 2007, the only complete year in the study period when new rotavirus vaccines were being used, the mortality rate was 1.4 per 1 million births.

The average ages of intussusception-associated mortality from 1979-1997 and in the most recent decade from 1998-2007 were 5.09 months and 5.07 months, respectively (t test, $P = .95$) (Figure 2). The intussusception-associated mortality rate decreased in the recent decade 1998-2007 in all age groups except the 5-month-old age group. Intussusception deaths in community settings declined from 55% in 1979 to 0% in 2007 with an overall downward trend (χ^2 test for trend, $P = .001$).

From 1998-2007, the intussusception mortality rate was similar among male and female children (2.3 per 1 million vs 2.0 per 1 million, respectively; relative risk [RR], 1.17;

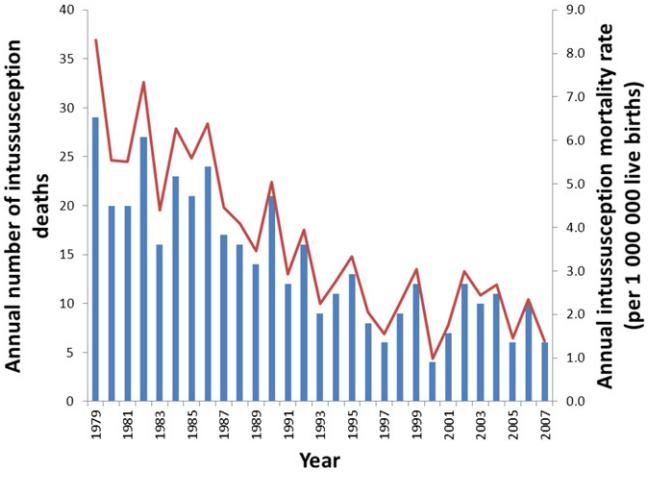

Figure 1. Intussusception mortality rate by year from 1979-2007 among infants in the US (*line*) and annual number of intussusception-associated infant deaths by year. (From NCHS. Mortality multiple cause of death files 1979-2007. http://www.cdc.gov/nchs/data_access/vitalstatsonline.htm. Last accessed June 15, 2011.)

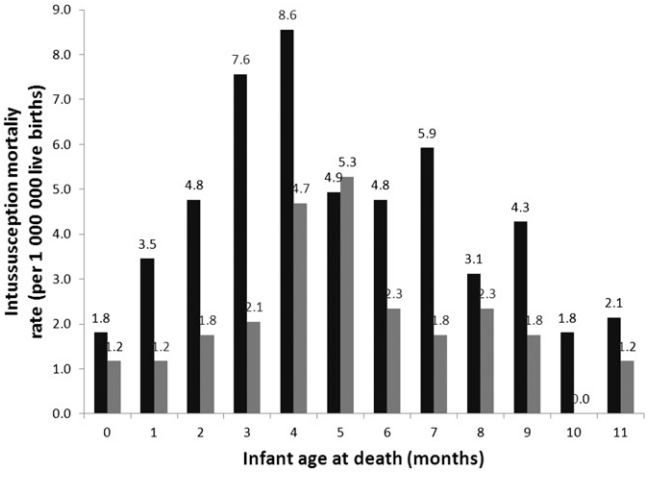

Figure 2. Intussusception mortality rate by infant age at death (months), 1979-1997 (*black bars*) and 1998-2007 (*gray bars*), US. (From NCHS. Mortality multiple cause of death files 1979-2007. http://www.cdc.gov/nchs/data_access/vitalstatsonline.htm. Last accessed June 15, 2011.)