

The Effectiveness of Child-Resistant Packaging for Aspirin

Gregory B. Rodgers, PhD

Objective: To evaluate the effectiveness of child-resistant packaging in reducing the mortality rate from the unintentional ingestion of aspirin for children younger than 5 years.

Design: Estimates of the annual aspirin-related mortality rate for children younger than 5 years in the United States were developed for the 1958-1990 study period. A multivariate negative binomial regression model was then used to estimate the independent effect of the packaging requirements on the child mortality rate during the postintervention period. The analysis controlled for changes in the per capita use of aspirin, long-term safety trends, and other extraneous and potentially confounding factors that may have affected the aspirin-related child mortality rate.

Main Outcome Measure: Estimated percentage reduction in the child mortality rate associated with the use of child-resistant packaging.

Results: After controlling for covariates, the use of child-resistant packaging was associated with a 34% reduction in the aspirin-related child mortality rate. This mortality rate reduction equates to the prevention of about 90 child deaths during the 1973-1990 postregulatory study period.

Conclusions: Child-resistant packaging has been effective in reducing aspirin-related child poisonings. However, because its effectiveness is only partial, further poison prevention strategies should be developed and instituted.

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DURING THE 1950s and 1960s, aspirin poisonings constituted a substantial poisoning hazard for children. From 1958 through 1963, for example, an annual average of about 120 fatal aspirin poisonings involved children younger than 5 years.¹ These poisonings accounted for slightly more than 25% of all fatal child poisonings involving the ingestion of solids and liquids and almost two thirds of fatal poisonings involving drugs.

Concern about the high incidence of aspirin poisonings inspired 2 Food and Drug Administration (FDA) conferences to address this hazard: the "Conference on the Accidental Ingestion and Misuse of Salicylate Preparations by Children" in 1955 and the "Conference on Prevention of Accidental Ingestion of Salicylate Products by Children" in 1966.^{2,3} It also provided a strong impetus for the Poison Prevention Packaging Act of 1970, which was designed to protect children younger than 5 years from poisonings caused by the unintentional ingestion of hazardous household substances.⁴

The Poison Prevention Packaging Act authorized the US Consumer Product Safety Commission to issue regulations requiring special child-resistant packaging for toxic substances used in or around the home. Aspirin was the first product covered by the new law; regulations requiring the use of child-resistant packaging for products containing aspirin became effective on August 14, 1972. The testing protocol required that at least 80% of children younger than 5 years be unable to open the safety packages within a specified time.⁵

An early postregulatory analysis evaluated trends in aspirin poisoning rates from 1965 through 1974 and concluded that child-resistant packaging for aspirin products had been effective in reducing aspirin-related poisonings in children.⁶ However, this finding was disputed in a widely publicized 1985 study based on a multiple regression analysis of the aspirin poisoning rate from 1963 to 1980.⁷ After controlling explicitly for potentially confounding influences, it found no statistical association between child-resistant packaging and the declining aspirin poi-

From the Directorate for Economic Analysis, US Consumer Product Safety Commission, Washington, DC.

soning rate; the author suggested that the earlier study failed to account for other factors that contributed to the declining rate of aspirin poisonings.

My article takes another look at the effectiveness of child-resistant packaging for aspirin products, based on a multivariate negative binomial regression analysis of fatal child poisonings during the period from 1958 to 1990. The negative binomial model is well suited for the analysis of data that have counts as possible outcomes. It can also be used to evaluate child-poisoning rates when the outcome data, measured in deaths, are indexed according to the population of children at risk. The 1958-1990 study period represents a substantially expanded database when compared with previous analyses.

SUBJECTS AND METHODS

DATA

Data on the annual number of child deaths caused by the unintentional ingestion of aspirin were collected from the files on underlying cause of death published by the National Center for Health Statistics (NCHS).¹ The NCHS data are classified by codes for external cause of death (E-codes) based on the standardized *International Classification of Diseases (ICD)* manuals of the World Health Organization.

The NCHS bases its classification of mortality data on the underlying cause of death reported in death certificates, which must be certified by physicians or other qualified persons such as medical examiners or coroners. Although the NCHS collected these data continuously during the study period, the specific E-codes according to which the aspirin-related deaths were classified vary because of revisions to the *ICD*. The *ICD-7*,⁸ which was applicable from 1958 through 1967, included aspirin deaths within E-code E872: "accidental poisonings by aspirin and salicylates." The *ICD-8*,⁹ which was applicable from 1968 through 1978, classified aspirin deaths within the 4-digit category E853.1, "salicylates and congeners," a subset of medications included in E-code E872 of the *ICD-7*. The category E853.1 explicitly excluded accidental deaths that were caused by methyl salicylate, *p*-aminosalicylic acid, and theobromine calcium salicylates, medications grouped with aspirin in the *ICD-7*. Finally, the *ICD-9*,¹⁰ which includes aspirin deaths within the category E850.1, "salicylates," also made several coding changes. Deaths caused by salicylamide, for example, were no longer grouped with those caused by aspirin.

Additional data used in the analysis comprised annual estimates of the US resident population¹¹ (including the population of children younger than 5 years), the annual domestic production of aspirin (which was available from 1958 to 1990),¹² and the unintentional-injury death rate from all causes for children younger than 5 years.¹³ The study period was limited to the years 1958 through 1990, the period for which data were available for all variables.

STATISTICAL ANALYSIS

The effect of child-resistant packaging on the child death rate was evaluated with a negative binomial regression model designed for rate data. In this model, the expected annual number of poisoning-related child deaths was assumed to follow a negative binomial distribution (with a log link) and was estimated as a function of predictor variables and an offset term.^{14,15} The offset term adjusted the expected value of the response variable for the population of children at risk and had a defined coefficient of 1.

As an alternative to the negative binomial model, a Poisson regression model was considered for the analysis but was rejected because the estimated response counts exhibited overdispersion (ie, a greater variability than would be expected with Poisson distribution). The negative binomial model is the standard parametric model used to account for overdispersion.¹⁶

The regression model included several predictor variables. The first was per capita US aspirin production (aspirin) in grams per year, a measure of risk exposure that should be directly related to the child mortality rate. Per capita aspirin consumption would have been preferable, but data on net aspirin imports were not available before 1967. However, during the time span when both production and consumption estimates were available, per capita aspirin production was highly correlated with aspirin consumption ($r=0.98$; $P<.001$).

A linear trend variable (trend=1 in 1958; trend=2 in 1959; . . . trend=33 in 1990) was included to control for long-term safety trends. These trends are reflected in the substantial decline in the unintentional death rate for children from all causes, from about 445 deaths per million children younger than 5 years in 1958 to approximately 136 deaths per million in 1997.¹³ This decline is related to factors such as improvements in emergency health care across time, improvements in the delivery of health information through health care providers and poison control centers, and the increased safety awareness of parents.^{17,18}

A categorical variable with a value of 1 beginning in 1982 was included to control for changing patterns in the consumption of aspirin following the discovery (and substantial publicity) of the relationship between children's use of aspirin and Reye syndrome.¹⁹

The primary variable of interest was regulation, a categorical variable that assumed a value of 1 beginning in 1973, the first full year of the packaging requirements. This variable should be negatively correlated with the child mortality rate if the presence of child-resistant packaging reduces child poisonings.

Finally, the model included 2 categorical variables, *ICD-7* and *ICD-8*, to represent the periods covered by these revisions to the *ICD* manuals relative to the ninth revision. The variable *ICD-7* equals 1 for 1958-1967 and 0 otherwise; *ICD-8* equals 1 for 1968-1978 and 0 otherwise.

An analysis was also conducted to measure the sensitivity of the statistical results to variations in the specification of the regression model.

RESULTS

After peaking at more than 7 deaths per million children younger than 5 years in the early 1960s, the aspirin-related child mortality rate declined substantially; by 1990, the mortality rate was less than 0.1 deaths per million (**Figure 1**). According to the regression results, the use of child-resistant packaging played a role in this reduction (**Table**). The results of the regression analysis were generally as expected. The child mortality rate was directly related to aspirin production and appears to have decreased beginning in the early 1980s following the discovery of the relationship between aspirin and Reye syndrome.

Long-term safety trends likely played a particularly important role in the declining mortality rate; the effect of the trend variable suggests an annual mortality rate reduction of about 5.6%. Additionally, the positive coefficients for the *ICD-7* and *ICD-8* categorical variables suggest higher mortality rates associated with the earlier classification periods. Besides being consistent with

the larger grouping of salicylate deaths included in the earlier ICD classification codes, these variables probably capture the higher mortality rates that resulted from therapeutic overdose during these earlier periods. Fatal aspirin poisonings due to overdoses mistakenly administered by parents or guardians constituted a documented and significant hazard pattern that was increasingly publicized and addressed during the 1960s.^{3,20}

Most important, the negative and significant coefficient for regulation suggests that child-resistant packaging independently lowered the child death rate by about 34% (95% confidence interval, 1%-55%) from levels that would have been expected in the absence of child-resistant packaging. This relationship is illustrated in **Figure 2**, which shows the predicted child death rate by year and the predicted mortality rates in the absence of requirements for child-resistant packaging. The figure is adjusted to exclude the positive death rate components associated with the ICD-7 and ICD-8 classification periods. It shows a declining mortality rate that was further reduced by child-resistant packaging. The relatively wide confidence interval for the regulation variable appears to be the result of intercorrelation between regulation and other predictor variables. Although this type of collinearity does not bias the coefficient estimates, it does tend to inflate the estimated SEs.²¹

An analysis was conducted to evaluate the sensitivity of the results to variations in the specification of the regression model. For example, when the unintentional-injury death rate from all causes for children younger than 5 years was substituted for the trend variable,¹³ the results suggested that child-resistant packaging reduced the child mortality rate by 41% (95% confidence interval, 3%-62%). Similarly, the results were not affected by reasonable variations in the categorical variable used to adjust for the discovery of the relationship between Reye syndrome and aspirin consumption; they were virtually identical when it was assumed that the discovery initially affected the poisoning rate in 1981 or 1983 rather than in 1982 (ie, when the categorical variable was set at 1 beginning in 1981 or 1983).

COMMENT

This study supports the conclusion that child-resistant packaging has played an important role in reducing the aspirin-related child death rate. After controlling for several extraneous and confounding variables that also affected the poisoning rate, child-resistant packaging was estimated to have reduced the aspirin-related mortality rate by about 34% relative to levels that would have been projected in the absence of child-resistant packaging. This 34% reduction equates to about 90 fewer child deaths during the 1973-1990 postregulatory study period.

The results of this analysis differ from those of the 1985 study by Viscusi,⁷ which did not find a statistical association between child-resistant packaging and fatal or nonfatal aspirin poisoning rates for children. The least-squares regression models used by Viscusi included a regulatory variable and an aspirin use variable, comparable with those used in our study. In addition, to account for

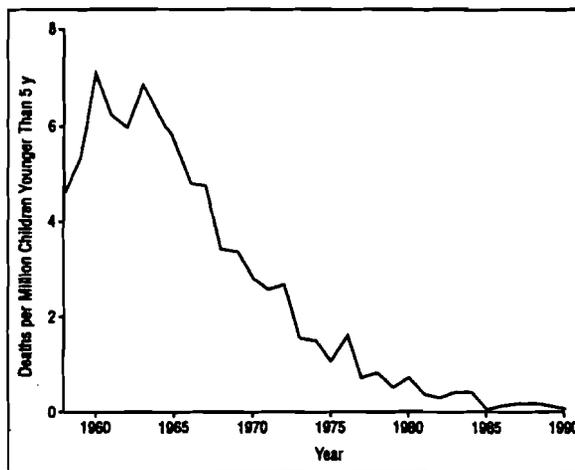


Figure 1. Child mortality rate associated with the ingestion of aspirin and other salicylates, 1958-1990.

Regression Results: Child Death Rate From the Accidental Ingestion of Aspirin, 1958-1990*

Variable	Coefficient (SE)†	Relative Risk (95% CI)
Intercept	-13.647‡ (0.399)	
Aspirin, g	0.015‡ (0.006)	1.015 (1.004-1.027)
Trend	-0.058‡ (0.019)	0.944 (0.906-0.978)
Regulation	-0.417‡ (0.198)	0.659 (0.449-0.989)
Reye syndrome	-0.526 (0.317)	0.591 (0.318-1.111)
ICD-7	0.961‡ (0.308)	2.615 (1.407-4.903)
ICD-8	0.549‡ (0.244)	1.731 (1.080-2.836)

*Deviance = 32.92, *df* = 26, and Pearson $\chi^2 = 1.11$. CI indicates confidence interval; ICD, *International Classification of Diseases*, and ellipses, not applicable.

†The relative risk minus 1 represents the percent change in mortality rate given a 1-unit increase in the predictor variable.

‡*P* < .05 using a 2-tailed test.

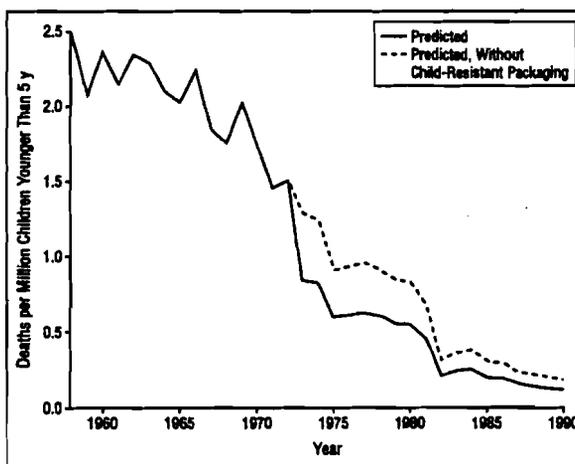


Figure 2. Predicted child mortality rate due to the ingestion of aspirin.

long-term trends, the models included both a lagged-response variable and another variable representing real per capita personal-consumption expenditures.

Several factors may help explain the lack of a statistical association found in the study by Viscusi. With

What This Study Adds

Because of the high incidence of aspirin poisonings, child-resistant packaging was required for aspirin shortly after the Poison Prevention Packaging Act was passed in 1970. Although this requirement has existed for almost 30 years, only 2 studies have attempted to quantify the effect of this packaging on aspirin poisoning rates. The most recent study, a highly publicized 1985 analysis, found no beneficial effect of child-resistant packaging on aspirin poisonings.

In contrast, our study finds that child-resistant packaging has played an important role in reducing the aspirin-related child death rate. This finding, combined with results from a recent study of oral prescription drug poisonings, supports a general conclusion that child-resistant packaging has been effective in preventing unintentional drug poisonings in children. However, despite the overall positive effect of this packaging, the results also suggest that it is only partially effective; therefore, further poison prevention strategies need to be developed.

respect to the analysis of mortality data, the regression model may have been affected by severe multicollinearity, as evidenced by the high intercorrelation exhibited between the predictor variables used in the analysis. Additionally, the lagged-response variable, which by definition was related to the response variable and therefore was highly correlated with it ($r=0.97$; $P<.001$), played such a dominant role in the analysis that it may have masked the effects of other variables. Finally, these problems may have been exacerbated by the relatively short study period in the analysis, which was limited to the evaluation of annual data from 1963 to 1980.

Also for 1963 to 1980, Viscusi evaluated nonfatal aspirin ingestions that were reported to the FDA's National Clearinghouse for Poison Control Centers by individual poison control centers. The same statistical factors that may have affected the analysis of fatal poisonings would also have affected the analysis of nonfatal ingestions. Additionally, according to the FDA, the data on nonfatal ingestions reported through the poison control centers were unsuitable for estimating population-based poisoning rates or secular trends of those rates. This was because participating poison control centers joined and left the reporting program periodically, many reported their data sporadically, and the size of the population served by participating poison control centers varied but was never measured (M. Fow, PhD, FDA, written communication, April 1987).

POSSIBLE LIMITATIONS

Despite the statistical significance and intuitive plausibility of the principal finding of our study—that child-resistant packaging has been effective in reducing the child mortality rate from aspirin products—the analysis must be interpreted with some caution. It does not explicitly adjust for changes in the consumption patterns of baby aspirin and other analgesics (such as acetaminophen),

for which little time series information is available, nor does it adjust for packaging changes adopted by aspirin manufacturers during the 1960s that may have influenced the poisoning rate. In 1966, for example, following the joint FDA-industry "Conference on Prevention of Accidental Ingestion of Salicylate Products by Children" highlighting the susceptibility of infants and young children to aspirin poisonings, the drug industry limited the number of children's aspirin tablets to 36 per bottle and expanded warning labels.³

Nevertheless, although these factors were not controlled for explicitly, there is no reason to believe that their exclusion invalidates the results. First, per capita aspirin use is the primary measure of risk exposure in aspirin-related deaths and, as shown in our study, was highly correlated with the child mortality rate. Second, including the trend variable to adjust for long-term safety improvements implicitly adjusts for the full range of factors that may have reduced the mortality rate smoothly across time, and may therefore account for factors such as expanded warning labels or long-term changes in the consumption patterns of other analgesics.

Finally, the results of this study are consistent with those of a recent analysis that found that the use of child-resistant packaging for oral prescription drugs reduced the mortality rate by about 45% from levels that would have been predicted in the absence of child-resistant packaging.²² This similarity supports our findings and provides additional evidence that child-resistant packaging is an effective countermeasure to unintentional child poisonings.

RECOMMENDATIONS FOR FURTHER RESEARCH

Although our study provides further indication that child-resistant packaging has effectively reduced child mortality rates from unintentional drug poisonings, the results also suggest that this effectiveness has been only partial. Consequently, additional strategies designed to prevent unintentional drug poisonings need to be developed and evaluated.

One strategy recently undertaken by the Consumer Product Safety Commission has been to increase consumer acceptance of child-resistant packaging by encouraging the development of packaging that is both child-resistant and easy for all adults to use.²³ Such packaging, which relies more on cognitive abilities than strength, should ultimately lead to further reductions in the child-poisoning rate by lowering adult resistance to the use of child-resistant packaging.

It would be useful to evaluate the effectiveness of packaging requirements for nondrugs such as furniture polish, paint solvents, turpentine, and other household products that are also covered by child-resistant packaging requirements. Although there is no reason to believe that child-resistant packaging for these products has been less effective than it has been for drugs, little effort has been made to quantify these effects.

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Corresponding author and reprints: Gregory B. Rodgers, PhD, Directorate for Economic Analysis, US Consumer Product Safety Commission, Washington, DC 20207 (e-mail:groddgers@cpsc.gov).

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