Why case-control studies showed no association between Sudden Infant Death Syndrome and vaccinations

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Abstract

Several case-control studies have frequently been cited to support the notion that vaccinations are not a risk factor of Sudden Infant Death Syndrome (SIDS). However, their findings are neither confirmed nor refuted by valid comparisons of incidence of SIDS in vaccinated infants to that reported in never vaccinated infants.

Keywords: case-control studies, vaccinations, Sudden Infant Death Syndrome (SIDS)

1. Introduction

Case-control studies [1-4] have frequently been cited to support the notion that vaccinations are not a risk factor of Sudden Infant Death Syndrome (SIDS). It is possible that the case–control design, used frequently to investigate risk factors for SIDS, can introduce unmeasured biases through both selection and exclusion of cases and controls [5]. For example, a case-control study from California, United States, found no association between prone sleeping and SIDS [6], but many other case control-studies found a significant association, and prone sleeping position was confirmed as a risk factor of SIDS in several cohort and case series studies [7-10]. Cause of SIDS is unknown, and infants who die from SIDS may have yet undiscovered underlying conditions that could have predisposed them to sudden death in infancy [11], while infants who survive, may not have such conditions. In a cohort study both vaccinated and never vaccinated groups would contain vulnerable and robust infants.

In spite of a careful search, I was unable to find a single published account of a population-based study where the incidence of SIDS was compared in vaccinated and never vaccinated infants. Because of the high vaccination rates in the U. S. and other developed countries, the small number of children that remains unvaccinated during the first year of life cannot represent a satisfactory control group [12].

The German case-control study published recently [13] has essentially the same design as studies [1-4].

It should be noted that in studies [1-4,13] infants who died suddenly are compared with living infants.

To facilitate calculation of measures of association, epidemiological data from case-control studies are often presented in a two-by-two-table [14].

Table 1. Presentation of data in a two-by-two-table from a case-control study.

	Disease (or Outcome)	
	Yes	No
Exposure Yes	*a*	*b*
Exposure No	*c*	*d*

In studies [1-4,13] outcome=SIDS, exposure=vaccination, individuals=infants.

Letters *a*, *b*, *c*, and *d* represent the following in a study sample:

- *a* = the number of vaccinated infants whose death was attributed to SIDS
- *b* = the number of living vaccinated infants
- *c* = the number of unvaccinated infants whose death was attributed to SIDS
- *d* = the number of living unvaccinated infants
- *T* = *a*+*b*+*c*+*d* – total number of study subjects.

Thus, from Table 1:
a+ *c*= the total number of SIDS victims in a study sample
b+*d* = the total number of living infants in a study sample

The sample estimate of the relative risk of SIDS among *vaccinated* study subjects calculated as univariate odds ratio (OR) for SIDS is expressed by the following formula:

$$OR = \frac{ad}{bc} \qquad (1)$$

An OR value of 1 implies that the outcome under investigation is equally likely in exposed and not exposed groups. In addtion, 1.0 is the null value for the relative risk (RR) estimate. An OR value that is <1 suggests that SIDS is *less likely* in vaccinated study subjects, and an OR value that is >1 suggests that SIDS is *more likely* in vaccinated study subjects.

The formula for the confidence interval (CI) for the relative risk calculated as odds ratio from a case-control study can be expressed as:

$$CI = \frac{ad}{bc}\exp[\pm z\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}] \qquad (2)$$

where *a*, *b*, *c*, and *d* in formula (2) are the numbers from Table 1. Moreover, since all the case-control studies in this review used a 95% confidence level for CI, *z* is 1.96 here.

The CI can provide all the information whether the association is statistically significant at a specified level. When the null value, 1.0, for the RR estimate is included in 95% confidence interval, then the corresponding *P*-value is, by definition,

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greater than 0.05, and the association is not statistically significant. When the null value is not included in this confidence interval, $P<0.05$ and the association being evaluated is considered to be statistically significant [14].

2. Results

I have noticed an interesting and persistent pattern: the overall proportion of vaccinated SIDS victims was always less than the proportion of vaccinated living controls. [1,3,4,13]

Studies [1-4,13] have fixed overall number of living controls per each SIDS victim.

Let $n = a+c$ be the total number of SIDS victims in a study sample; $m = b+d$ be the total number of living control infants in a study sample.

Let $k = \frac{m}{n}$ - number of controls per SIDS case, k does not have to be an integer and $m=kn$.

Let $p = \frac{a}{a+c} = \frac{a}{n}$

be the proportion of vaccinated SIDS victims.

Analogously

$$q = \frac{b}{b+d} = \frac{b}{kn}$$

is the proportion of vaccinated living infants in a study sample. Then

$$a=pn$$
$$b=qkn$$
$$c=n-a=n-pn=(1-p)n$$
$$d=kn-b=kn-qkn=(1-q)kn.$$

Thus, Table 1 can be rewritten as shown in Table 2.

Table 2. Presentation of data in a two-by-two-table from a case-control study in terms of proportions of vaccinated study subjects with a fixed number of cases per control.

	SIDS	
	Yes	No
Vaccinated	*pn*	*qkn*
Unvaccinated	*(1-p)n*	*(1-q)kn*

Using the Table 2 entries, expression (1) becomes:

$$OR = \frac{pn(1-q)kn}{(1-p)nqkn} = \frac{(1-q)p}{(1-p)q} \qquad (2)$$

and

$$\text{OR}<1, \text{ whenever } \frac{(1-q)p}{(1-p)q} < 1 \qquad (3)$$

Solving inequality (3), we obtain

$$(1-q)p<(1-p)q$$
$$p-qp<q-pq$$
$$\boldsymbol{p<q}$$

Thus, whenever the proportion p of vaccinated SIDS cases is less than the proportion q of living vaccinated controls, it guarantees that the sample estimate of the univariate OR will be less than one. [**Note:** This result depends only on the proportions p and q and does not depend on the number of cases and number of controls per case, study SIDS definition, vaccine brand, number of vaccines administered simultaneously, etc.]

When, in addition, the upper bound of 95% CI is less than 1.0, the result can be simplistically interpreted as vaccination may even lower risk of SIDS.

Table 3 reflects the overall reported proportions of vaccinated SIDS cases and living controls (p and q), and k—the number of cases per control in studies [1,3,4,13]. The overall proportions of vaccinated SIDS victims and vaccinated controls cannot be determined directly from the New Zealand study [2].

Table 3. Overall proportions *p* and *q* of vaccinated SIDS victims and vaccinated living infants; *k* is the number of controls per SIDS case

Study	*p*, %	*q*, %	*k*
U. S. NICHHD [1]	39.8	55 (control A), 53.2 (control B)	2
French [3]	12[a]	14[a]	3
U. K. CESDI SUDI [4]	49	67	4
German GeSID [13]	50	60	3

[a]Proportions of infants who received DTP, Polio with or without Hib vaccine

Additionally, the proportion of vaccinated SIDS victims was less than the proportion of vaccinated living controls within each age group under investigation [1,3], within all age groups except birth to under 6 weeks in New Zealand study [2], within all age groups except 4-month-old and over 6 months in German study [13], and across all strata in the U.K. study [4].

The formula for the Mantel-Haenszel pooled estimate of the relative risk for a case controls study is given by [14]:

$$\text{RR}_{\text{MH}} = \frac{\sum \frac{ad}{T}}{\sum \frac{bc}{T}} \qquad (4)$$

where summation in the numerator and in the denominator is performed separately over each individual strata. Whenever $p<q$ in a stratum, $ad<bc$, $\frac{ad}{T} < \frac{bc}{T}$ and, consequently, RR_{MH} is <1. The corresponding 95% confidence interval is

$$95\%\ \text{CI} = \text{RR}_{\text{MH}}\left(1 \pm 1.96 / \sqrt{\chi^2_{MH}}\right) \qquad (5)$$

$$\text{where } \chi^2_{MH} = \frac{[\sum a - \sum \frac{(a+b)(a+c)}{T}]^2}{\sum \frac{(a+b)(c+d)(a+c)(b+d)}{T^2(T-1)}} \qquad (6)$$

It should be noted that any positive power of a number from the interval (0, 1) also belongs to the interval (0,1). Thus, whenever $\sqrt{\chi^2_{MH}} \geq 1.96$ in expression (5), and $0 < \text{RR}_{\text{MH}} < 1$, the 95% CI will not contain 1.0, and result will be interpreted as "vaccination may even lower the risk of SIDS."

This was precisely the case in the U.K. study across all strata [4]. In the French study [3] the odds ratio for infants vaccinated with DTP, polio, with or without Hib vaccine multivariate odds ratio of SIDS became 1.08 for vaccinated infants and 95% CI

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was 0.49 to 2.36. The authors in the French study concluded that DTP, polio, with or without Hib vaccines are not a risk factor of SIDS. However, because the 95% CI includes 1.0, the authors' own calculations actually support the conclusion that the study neither proved nor disproved whether vaccination is a risk factor of SIDS.

Similarly, the proportion of vaccinated SIDS cases was greater than the proportion of vaccinated living controls in the age group birth-under 6 weeks when hepatitis B and BCG vaccines are given in the New Zealand study [2]. There, the authors stated: "There was no increased risk of SIDS for infants who had not been immunized at birth". [2] However, since the univariate odds ratio of SIDS was 0.9 for unvaccinated infants aged birth to 6 weeks, and 95% CI (0.7, 1.1) contains 1.0, it is impossible to conclude whether vaccination (or absence of one) is a risk factor of SIDS in this age group in the study sample [2].

One of the published rapid responses to the study by Fleming *et al.* [4] has mentioned that one cannot rely upon such case-control studies alone to either prove or disprove an association between vaccination and SIDS [15].

The first dose of the primary series of vaccines was recommended at age 6 weeks in New Zealand [2] and at 2 months in the United States [1], France [3], United Kingdom [4], and Germany [16]. Vaccination coverage among 6-week-old New Zealand study infants was high: 83.5% of the SIDS cases and 91.5% of controls were vaccinated. Since the choice of a case-control study is based on the fact that, when vaccination coverage is high, a cohort study is not an option, it is unclear why only 12% of cases and 14% controls aged 30-90 days were vaccinated in the French study [3]. There was no explanation why in the NICHHD study [1] only 27% of the SIDS cases and 34% of control infants younger than 3 months were vaccinated. Similarly, in the CESDI SUDI study 21% of the SIDS cases and 34% of controls aged 0-3 months were vaccinated [4]. In the German study 16% of SIDS cases and 23% of controls younger than 3 months were vaccinated [13].

Does it follow that, in four out of five countries where the studies were conducted, unvaccinated infants under age 3 months were more likely to be enrolled in the studies than vaccinated infants? Or were younger infants in these four countries consistently behind in their vaccination schedule? Or was the NICHHD study [1] design *adopted in all subsequent publications*, "knowingly designed" to demonstrate that such "well-designed" epidemiological studies "consistently" show no association between SIDS and vaccines?

In most studies [1,2,4,13], the authors concluded that the observed number of SIDS cases did not exceed the "expected" number that had been derived from vaccinated population.

3. Conclusion

Systematic inclusion of higher proportions of vaccinated living controls in case-control studies which investigated association between SIDS and vaccines as well as unusually low vaccination coverage among study infants younger than 3 months in all but one reviewed study constitutes potential selection bias.

Thus, the finding: "The evidence is inadequate to accept or reject a causal relation between SIDS and vaccines" is more scientifically sound and appropriate than the conclusion the Institute of Medicine committee published in their 2003 report:

> "The evidence does not support a causal link between sudden infant death syndrome (SIDS) and either the diphtheria, tetanus, and whole-cell pertussis (DTwP) vaccine or exposure to multiple childhood vaccines." [17]

References

[1] Hoffman HJ, Hunter JC, Damus K, Pakter J, Peterson DR, van Belle G, *et al.* Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. Pediatrics 1987;79(4):598–611.

[2] Mitchell EA, Stewart AW, Clements M, Ford RPK. Immunisation and the sudden infant deaths syndrome. Arch Dis Child 1995; 73(6): 498–501.

[3] Jonville-Bera AP, Autret-Leca E, Barbeillon F, Paris-Llado J; French Reference Centers for SIDS. Sudden unexpected death in infants under 3 months of age and vaccination status—a case-control study. Br J Clin Pharmacol 2001;51(3):271–6.

[4] Fleming PJ, Blair PS, Platt MW, Tripp J, Smith IJ, Golding J. The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study. BMJ 2001;322(7290):822–5 http://www.bmj.com/cgi/content/full/322/7290/822

[5] Mezei G, Kheifets L. Selection bias and its implications for case–control studies: a case study of magnetic field exposure and childhood leukemia. Int J Epidemiol 2005; 35:397–406

[6] Klonoff-Cohen HS, Edelstein SL. A case-control study of routine and death scene sleep position and sudden infant death syndrome in Southern California. JAMA 1995 Mar. 8; 273(10):790–4.

[7] Daltveit AK, Oyen N, Skjaerven R, Irgens LM. The epidemic of SIDS in Norway 1967–93: changing effects of risk factors. Arch Dis Child 1997 Jul.;77(1):23–7.

[8] Blair PS, Sidebotham P, Berry PJ, Evans M, Fleming PJ. Major epidemiological changes in sudden infant death syndrome: a 20-year population-based study in the U.K. Lancet 2006 Jan. 28;367(9507):314–9.

[9] Kerbl R, Zotter H, Einspieler C, Roll P, Ratschek M, Kostl G, et al. Classification of sudden infant death (SID) cases in a multidisciplinary setting. Ten years experience in Styria (Austria). Wien Klin Wochenschr 2003 Dec. 30;115(24):887-93.

[10] Dwyer T, Ponsonby AL, Newman NM, et al. Prospective cohort study of prone sleeping position and sudden infant death syndrome. Lancet 1991;337:1244–7.

[11] Guntheroth WG, Spiers PS. The triple risk hypotheses in sudden infant death syndrome [review]. Pediatrics 2002;110:e64.

[12] Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. Public Health Rep. 1997;112:10–21.

[13] Vennemann MM, Butterfass-Bahloul T, Jorch G, Brinkmann B, Findeisen M, Sauerland C, Bajanowski T, Mitchell EA, The GeSID group. Sudden infant death syndrome**:** no increased risk after immunization. Vaccine 2007 Jan 4;25(2):336–40.

[14] Hennekens CH; Buring JE; Mayrent SL. Epidemiology in medicine. 1987 1st ed. Little, Brown and Company Boston/Toronto; ISBN: 0316356360 (pbk.) 9780316356367 (pbk.)

[15] White H. SIDS and the link with vaccination. Rapid Response to Fleming PJ, *et al* http://www.bmj.com/cgi/eletters/322/7290/822#14749. 2001; May 28.

[16] von Kries R, Toschke AM, Strassburger K, Kundi M, Kalies H, Nennstiel U, *et al.* Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilius influenzae type b: is there a signal? Eur J Pediatr 2005; 164(2):61–9.

[17] Stratton K, Almario DA, Wizemann TM, McCormick MC, eds. Immunization Safety Review Committee. Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy. Institute of Medicine 2003. ISBN: 0-309-08886-0.

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